Peacock, A., Tran, L. T., Larney, S., Stockings, E., Santo Jr , T., Jones, H. E., Santomauro, D., & Degenhardt, L. (2020). All-cause and cause-specific mortality among people with regular or problematic cocaine use: A systematic review and meta-analysis. *Addiction*. https://doi.org/10.1111/add.15239

ADDICTION SSA SOCIETY FOR THE STUDY OF ADDICTION

All-cause and cause-specific mortality among people with regular or problematic cocaine use: A systematic review and meta-analysis

Journal:	*Addiction*
Manuscript ID	ADD-19-1080.R2
Manuscript Type:	Review
Date Submitted by the Author:	03-Aug-2020
Complete List of Authors:	Peacock, Amy; University of Tasmania, National Drug and Alcohol Research Centre Tran, Lucy; University of NSW, National Drug and Alcohol Research Centre Larney, Sarah; University of New South Wales, NDARC Stockings, Emily; University of New South Wales, National Drug and Alcohol Research Centre Santo Jr, Thomas; University of New South Wales, NDARC Jones, Hayley; University of Bristol, Population Health Sciences, Bristol Medical School Santomauro, Damian; The University of Queensland, Queensland Centre for Mental Health Research and and School of Public Health Degenhardt, Louisa; University of NSW, National Drug and Alcohol Research Centre; University of Melbourne, School of Population and Global Health
SUBSTANCE:	stimulants
METHOD:	Meta-analyses
FIELD OF STUDY:	epidemiology
Keywords:	cocaine, mortality, injury, homicide, cardiovascular, infectious disease, suicide

All-cause and cause-specific mortality among people with regular or problematic cocaine use: A systematic review and meta-analysis

Amy Peacock[1,2], Lucy Thi Tran[1], Sarah Larney[1], Emily Stockings[1], Thomas Santo Jr[1], Hayley Jones[3], Damian Santomauro[4,5] & Louisa Degenhardt[1]

[1]National Drug and Alcohol Research Centre (NDARC), University of New South Wales, Sydney, Australia

[2]School of Psychology, University of Tasmania, Hobart, Australia

[3]Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, England

[4]Queensland Centre for Mental Health Research and School of Public Health, University of Queensland, Brisbane, Australia

[5]Institute for Health metrics and Evaluation, University of Washington, Washington, USA

Current word count: 3966

Declarations of competing interests: AP has received investigator-initiated untied educational grants for studies of opioid medications in Australia from Seqirus and Mundipharma. SL has received investigator-initiated untied educational grants for studies of opioid medications in Australia from Indivior. LD has received investigator-initiated untied educational grants for studies of opioid medications in Australia from Indivior, Mundipharma and Seqirus.

Funding: The National Drug and Alcohol Research Centre is supported by funding from the Australian Government Department of Health under the Drug and Alcohol Program. DS is affiliated with the Queensland Centre for Mental Health Research which receives core funding from the Department of Health, Queensland Government. SL and LD are supported by NHMRC Fellowships (GNT1140938 and GNT1135991) and by National Institute of Health (NIH) grants National Institute on Drug Abuse (NIDA) (R01DA1104470). ES is supported by an NHMRC Fellowship (GNT1104600). AP is supported by an

NHMRC Fellowship (GNT1109366). HEJ was supported by an MRC Career Development Award in Biostatistics (MR/M014533/1).

Corresponding author: Dr Amy Peacock, Senior Research Fellow, National Drug and Alcohol Research Centre, University of New South Wales, 22-32 King St, Sydney 2052, Australia. Email: Amy.Peacock@unsw.edu.au; Phone: +61 2 9385 0282.

ABSTRACT

Aims: To estimate pooled all-cause and cause-specific mortality risk for people with regular or problematic cocaine use.

Methods: Systematic review and meta-analysis of prospective or retrospective cohort studies (n≥30) of people with regular or problematic cocaine use with data on all-cause or cause-specific mortality. Of 2808 papers, 28 were eligible and reported on 21 cohorts with a total 170,019 individuals. Cohorts identified based on acute care for drug poisoning or other severe health presentation were excluded. Title/abstract screening was conducted by one reviewer; a second reviewer independently checked 10% of excluded studies. Two reviewers conducted full-text screening. Data were extracted by one reviewer and checked by a second. A customised review-specific study reporting quality/risk of bias tool was used. Data on crude mortality rates (CMR) and standardised mortality ratios were extracted for both all-cause and cause-specific mortality. Standardised mortality ratios were imputed where not provided by the author using extracted data and information from the Global Burden of Disease Study 2017. Data were pooled using a random-effects model.

Results: The pooled all-cause crude mortality rate was 1.24 per 100 person-years (95% CI: 0.86, 1.78; n=16 cohorts), but with considerable heterogeneity (I^2=98.8%). The pooled all-cause standardised mortality ratio was 6.13 (95%CI: 4.15, 9.05; n=16 cohorts). Suicide (SMR 6.26, 95%CI 2.84, 9.68), accidental injury (SMR 6.36, 95%CI 4.18, 9.68), homicide (9.38, 95%CI 9.38, 3.45, 25.48), and AIDS-related mortality (SMR 23.12, 95%CI 11.30, 47.31) were all elevated compared with age and sex peers in the general population.

Conclusions: There are elevated rates of mortality among people with regular or problematic cocaine use for traumatic deaths and deaths attributable to infectious disease.

Review registration: PROSPERO CRD421018094623

Keywords: cocaine; mortality; injury; homicide; cardiovascular; infectious disease; suicide

INTRODUCTION

Cocaine manufacture is estimated to be at the highest level recorded and trafficking routes continue to expand globally (1). Greater availability has been accompanied by increased use, with an estimated 0.37% (CI 0.31-0.42) of adults aged 15-64 years reporting use globally in 2017, equivalent to 18.0 (CI 15.5-21.0) million people (1). Confluence of increasing availability and demand, coupled with indicators of increasing purity in some regions (1, 2), creates a higher risk environment for increased problematic use and health harms.

The most common forms of cocaine are hydrochloride salt (typically a fine white powder) and base ('crack' cocaine), the latter appearing crystal- or rock-like and typically being higher purity (3). Cocaine produces stimulant effects, increasing heart rate and blood pressure, enhancing alertness and producing feelings of euphoria, with a half-life of 30-60 minutes (4). Regular use of cocaine is associated with adverse health effects, predominantly cardiovascular (e.g., arrhythmia, myocardial infarction, stroke) and psychiatric (e.g., psychotic episodes, suicidal ideation) in nature (5, 6). There are additional and greater severity health risks depending on route of administration, including respiratory problems with smoking (6), nasal ulceration with snorting (7) and bloodborne virus transmission with injection, as well as via form used (e.g., higher risk of dependence with crack versus powder cocaine; 6).

A systematic review of studies published until 2008 suggested that people with regular cocaine use had a four to eight times higher mortality risk than their age and sex peers in the general population(8). Only seven cohorts were located, so a lack of data precluded quantifying risks of cause-specific mortality or examination of reasons for variation in mortality rates. In the intervening period, there has been significant research exploring specific harms associated with cocaine use from which cause-specific mortality estimates could be computed. Increased cocaine supply and demand globally and increasing poisoning deaths in a number of countries (e.g., United States; 9), including the highest rate of deaths in England and Wales observed in 2017 (10), makes it imperative that the magnitude of

mortality risk by cause be quantified for this population. As such, the aims of this systematic review were to:

1. Update the previous systematic review and perform meta-analysis to calculate pooled estimates of all-cause crude mortality rates (CMRs) and standardised mortality ratios (SMRs) for people with regular or problematic cocaine use globally (regardless of treatment status); and
2. Compute pooled estimates of cause-specific CMRs and SMRs, with a focus on those causes of death that could be causally related to regular or problematic cocaine use.

METHODS

We report the systematic review methodology in accordance with the PRISMA guidelines (11) (**Appendix A**). This review protocol was registered with PROSPERO (CRD42018094623; **Appendix B**).

Search strategy and study screening

Medline, Embase and PsycINFO peer-reviewed literature databases were searched using the OVID™ interface/platform for articles published between 2009 and 22 February 2018. Relevant articles published between 1980 and 2008 were identified through a previous review conducted by the research team (8). In line with the previous review, search strings incorporating keywords and Medical Subject Headings (MeSH terms) related to cocaine/crack cocaine and mortality epidemiology were used to identify relevant articles (see **Appendix C and D**). Searches were limited to human literature. There were no restrictions on publication type or language; papers published in languages other than English were read via Google Translate or by a team member fluent in the language.

Citations were imported into an Endnote™ library where duplicate citations were removed, and imported into Covidence, a web-based screening tool (12). Titles and abstracts were reviewed by one team member (LTT or research assistants); 10% of excluded studies were checked by a second person (AP) to monitor accuracy. Full-text articles were reviewed by two reviewers (LTT and AP or LD); discrepancies were resolved by a third reviewer (AP or LD). Reference lists for relevant systematic reviews identified in the peer-review literature search were hand searched for additional papers not already identified.

Study eligibility

Studies were included if they were cohort or case-control studies or clinical trials (n≥30 people) where: i) at least 90% of the sample reported regular or problematic use of cocaine and ii) data on all-cause or cause-specific CMRs or SMRs were available (see **Appendix E** for detailed inclusion and exclusion criteria). This could include cohorts that were identified based on criteria other than cocaine use but

reported mortality data for a sub-group of people reporting regular or problematic cocaine use. Cohorts were defined as comprising people with regular or problematic use if individuals reported cocaine as their primary drug used, cocaine injection, cocaine dependence, treatment for cocaine dependence or other healthcare presentation related to the effects of cocaine. Cohorts defined by any cocaine use (with no other indicators of cocaine-related problems) were excluded. Cohorts defined by cocaine overdose/poisoning or other serious adverse health presentations with high mortality risk were excluded. This included cohorts defined by cardiovascular presentations related to cocaine exposure or HIV positive status; estimates from these studies are available in **Appendix F**.

Data extraction

The data extraction worksheet was developed in Microsoft Excel based on the previous review. extraction was standardised through the use of a manual detailing data entry rules (8). Data were independently extracted by one reviewer (LTT) and checked by a second reviewer (TS).

Variables extracted included study information (e.g., country of sample, length of follow-up, recruitment setting) and sample information (e.g., age, sex, percentage of sample injecting, percentage engaged in treatment, form of cocaine used). With respect to the outcomes of interest (all-cause and cause-specific mortality), we extracted sample size, number of observed deaths (all-cause and cause-specific), person-years of observation, CMRs and SMRs. Data were extracted for specific causes of death which might be causally related to regular or problematic cocaine use through direct acute or chronic effects of the drug, or indirectly via other risk pathways (e.g., use of non-sterile injection equipment, high risk sexual behaviours). These causes of death comprised: drug-related, accidental injury, suicide, homicide, cardiovascular disease, respiratory disease, cancer, AIDS-related and digestive disease (the latter including liver diseases)(6). We also extracted International Classification of Diseases (ICD) codes or other information used to define cause-specific mortality. Where data for a study were incomplete, other published papers using the same cohort were sourced

to locate missing data. If supplementary information could not be located or did not detail the data needed, authors were contacted by email for additional information.

Quality of reporting and risk of bias

There are no standard tools available for assessing risk of bias in descriptive studies reporting estimates of CMRs or SMRs. However, risk of bias tools for observational studies assessing the effects of exposures are under development and some domains of these tools are clearly relevant (13). We assessed risk of bias for the two domains that we considered most relevant for this type of study design: sample representativeness (i.e., the number of site locations and sample types) and outcome measurement (i.e., ascertainment of death by death registry/certificate versus indirect sources). Studies were rated as being at higher or lower risk of bias on these domains. The tool also measured three components of study reporting quality, comprising cohort description (i.e., age and/or sex data for the cohort), data completeness (i.e., numerator and denominator for outcome variable) and definition of cause-specific deaths (i.e., ICD codes or other information to define cause of death). Studies were assessed as having higher or lower risk or bias or quality reporting on each of these domains (see **Appendix G** for full details of tool).

Data analysis

Calculation of CMR, SMR, and relative risks

If not reported by study authors, CMRs were calculated as per 100 person-years (100PY). Where person-years were not reported nor made available by the authors, an imputed CMR follow up calculation was undertaken using other data reported by the authors. This calculation was based on the assumption that deaths occurred halfway through the follow-up period so that each person who died contributed half the person-year follow-up of survivors (see Appendix H for formula and example computation).

Standardised mortality ratios (SMRs) represent the CMR ratio between those exposed to the risk and the general population (including those exposed to the risk). If not reported by study authors, SMRs were calculated by dividing the sample CMR by the CMR for the for the respective age, sex, location, and years from the Global Burden of Disease (GBD) 2017 study (14). The GBD 2017 study used vital registration, verbal autopsy, registry, survey, policy, and surveillance data to model mortality estimates for 282 causes of death in 195 countries and territories. Due to the nature of GBD data classification, a match between the GBD database and study classification for respiratory and digestive disease mortality was unable to be obtained resulting in CMRs being unable to be converted into SMRs. Standard errors of log-transformed CMRs and SMRs were estimated using Rothman Greenland method (15).

Relative risks (RRs) comprise the ratio of mortality risk between those exposed to the risk (i.e., regular or problematic cocaine use) and those not exposed to the risk. With a low prevalence exposure such as regular and/or problematic cocaine use, SMRs and RRs should be similar, but RRs provide an estimate that is useful for further estimation of burden of disease. RRs were estimated from SMRs using the method described by Jones and Swerdlow (16) by adjusting the SMR by the proportion of the general population that experiences cocaine dependence (see **Appendix H** for the formulae).

Pooling all-cause and cause-specific mortality CMR and SMR

DerSimonian and Laird random-effects meta-analysis (17) was conducted in STATA version 14.2(18) to pool all-cause and cause-specific CMR and SMR estimates. This allows for heterogeneity between and within studies (noting that each study could only contribute one estimate to each meta-analysis). Heterogeneity was quantified using the I^2 statistic and described as low (≤30%), moderate (>30% and ≤50%), substantial (>50% and ≤90%) or considerable (>75% and 100%)(19).

Understanding variation in CMR and SMR

Sources of heterogeneity in all-cause CMR and SMR were investigated through univariate meta-regressions, including aspects of the study design (including the percentage of the cohort that was

female, type of cocaine used, and geographical region) and the characteristics of the sample (including year of final follow-up, and recruitment setting). Variables were only included in meta-regressions if 5 or more data points were available per variable.

Sensitivity analyses

We undertook several addition analyses to examine potential impacts of our imputed metrics (CMRs, person years, SMRs) for studies that did not report all of these metrics upon the estimates generated in our meta-analyses. First, we generated estimated person years and CMRs for studies using our methods described above for studies that had reported all of these and compared the resulting estimates with the author-reported estimates; we found reasonable consistency for four out of seven studies (**Appendix H)**. Second, we compared pooled estimated CMRs that included studies with imputed CMRs with the pooled estimates that only included author-reported CMRs. Finally, we contrasted the pooled estimated SMRs including studies where we used derived SMRs with pooled estimates that only used author-reported SMRs.

RESULTS

As evident in the PRISMA study flow diagram in **Figure 1**, the search identified 2,808 papers, of which 209 were screened in full. Of these 28 papers were deemed eligible, including 21 cohorts reported in primary publications and 7 secondary publications providing additional data for those cohorts reported in the primary publication (see **Appendix I** for excluded studies and **Table 1** for details of included studies).

All cohorts (or subsample of cohorts) included here wholly comprised people who reported regular or problematic cocaine use (see **Appendix J).** Cohort size ranged from 63 to 83,808 individuals (total 170,019 individuals) and follow up of the cohort ranged between 58 to 468560 PY (total 1,012,147 PY). Cohorts were recruited from nine countries: eight of which were classified as high-income and one (Brazil) as middle-high income. Over two-fifths of the cohorts (43%, n=9) were recruited from the United States, three cohorts from Spain and two from Denmark. Relative to the previous review (9 cohorts)(8), 13 new cohorts were identified and three cohorts had additional published follow-up data. One study(20) from the original review was excluded as, on review for the current study, the population was not identified as reporting regular or problematic cocaine use.

[Figure 1 here]

[Table 1 here]

Risk of bias and study reporting quality

Two-fifths (42.9%) of the cohorts were at risk of bias from poor representativeness; that is, the sample were recruited from a single site location or from a single sample type (e.g., people who were in treatment; see **Table 2**). Only three cohorts (14.9%) did not use an official death registry to identify deaths within the cohort, suggesting low risk of bias in outcome ascertainment.

Outcomes for quality of reporting were mixed. Both age and sex characteristics of the cohort were reported for all except three cohorts (14.9%). However, half (52.4%) of the cohorts had incomplete

mortality data, where the numerator or denominator for the main analyses of mortality were not reported. Of the 17 cohorts for whom cause-specific mortality was reported, 10 (58.8%) did not provide definition(s) of the cause of death (see **Appendix J** for ICD codes used).

[Table 2 here]

It is important to note that quality of reporting outcomes was assessed for the total cohort. In many instances, people with regular or problematic cocaine use were a subsample of a larger cohort of people who use drugs. Age/sex characteristics and both numerator and denominator for mortality specifically for the sample who report regular or problematic cocaine use were thus only available for 8 (38%) and 5 (24%) cohorts, respectively (**Table 2**).

All-cause mortality

Data from 16 cohorts yielded an all-cause CMR of 1.24 per 100 PY (95% CI: 0.86, 1.78) with substantial heterogeneity (I^2=98.8%) (**Table 3; Figure 2**). Meta-regression analyses to explore sample and study characteristics that could explain high heterogeneity showed that the percentage of the cohort reporting injecting drug use was positively associated with higher CMRs (**Table 4; Appendix L**). Similarly, recruitment of the cohort from a single city (versus subnational/national recruitment) was associated with higher CMRs. There was little or no statistical evidence of an association of CMR with other variables explored (**Table 4**).

[Figure 2 here]

Authors of studies for seven cohorts reported all-cause SMRs; we imputed all-cause SMRs for a further 9 cohorts. The pooled all-cause SMR across the 16 cohorts was 6.13 (95%CI: 4.15, 9.05), with substantial heterogeneity (I^2 = 99.0%) (**Table 3, Figure 2**). This estimate was similar to that observed from the seven cohorts where all-cause SMRs were reported by the authors (5.58, 95%CI: 3,90, 7.99; I^2 = 96.6%) (**Appendix L**). Excess mortality was particularly elevated among cohorts reporting lifetime injecting (13.74, 95% CI: 12.67, 14.90; I^2=91.2%; n=5 cohorts).

[Table 3 here]

The percentage of the cohort that was female was negatively associated with excess mortality (**Table 4; Appendix L**). Study characteristics associated with excess mortality comprised recruitment setting (with higher SMRs for cohorts recruited from hospital versus treatment services and other settings) and sampling frame (with higher SMRs for cohorts recruited from a single city versus subnational/national recruitment).

[Table 4 here]

Drug-related deaths

Eight cohorts reported data on drug-related deaths. The definition of drug-related deaths was not provided for six cohorts; for the remaining two cohorts, 'drug-related deaths' comprised poisoning deaths, deaths attributed to mental and behavioural disorders due to psychoactive substance use, and deaths from other causes that were thought to be drug-related by the authors following consultation with forensic and toxicological services (e.g., ICD-10 code J81 'pulmonary oedema')(21). The pooled drug-related CMR was 0.34 per 100PY (95%CI: 0.10, 1.15), again with considerable heterogeneity (I^2 = 98.6%) (**Table 3, Figure 3**). SMRs were only reported for two cohorts, with a very high pooled estimate observed (44.37, 95% CI: 37.28, 52.81; I^2=63.7%) (**Appendix L**). We have not reported the pooled estimate for all cohorts - including those for whom we imputed SMR as the estimate was deemed unstable.

[Figure 3 here]

Traumatic deaths: suicide, accidental injury, and homicide

The pooled suicide CMR was 0.07 per 100PY (95%CI: 0.04, 0.10; I^2=72.6%; n=8 cohorts), with both pooled accidental injury (n=6 cohorts) and homicide (n=3 cohorts) CMR estimated at 0.09 per 100PY (95%CI: 0.04, 0.22; I^2=95.4% and 95%CI: 0.01, 1.54; I^2=98.4% respectively) (**Table 3, Figure 3**). The pooled SMR based on author-reported and imputed estimates was 6.26 (95% CI: 2.84, 13.80; I^2=94.4%)

for suicide, 6.36 (95% CI: 4.18, 9.68; I^2=71.9%) for accidental injury and 9.38 (95% CI: 3.45, 25.48; I^2=90.1%) for homicide (**Table 3, Figure 4**). Pooled estimates of the subsample of author-reported SMRs were higher for suicide and lower for accidental injury and homicide (**Appendix L**) but fell within the confidence intervals of the former estimates. There was substantial heterogeneity in these pooled CMR and SMR estimates.

AIDS-related deaths

The pooled CMR for AIDS-related deaths based on 6 cohorts was 0.28 per 100PY (0.12-0.63; I^2 = 95.1%) (**Table 3, Figure 3**). Only one study reported a SMR for AIDS-related deaths, with an excess mortality rate five times that expected in the general population (4.98, 95% CI 0.70, 35.34; **Appendix L**). The pooled SMR based on author-reported and imputed estimates was higher (23.12, 95%CI 11.30-47.31; I^2 = 90.1%; n=6 cohorts) (**Table 3, Figure 4**) but fell within the confidence interval for the former estimate.

Digestive disease deaths

The pooled CMR for digestive diseases based on three cohorts was 0.14 per 100PY (95%CI: 0.03, 0.73; I^2 = 96.1%). The SMR was only reported by authors for one cohort (1.90, 95%CI 1.20, 2.89). Three different cohorts provided CMRs and SMRs for liver-specific deaths, with these deaths occurring more than three times the expected rate (pooled SMR: 3.36, 95%CI 0.51, 22.10; I^2 = 92.5%; n=3 cohorts) (**Table 3, Figure 4**).

Other causes of death

Pooled CMRs were derived from four cohorts for cardiovascular disease (0.13 per 100PY; 95%CI: 0.07, 0.24; I^2 = 77.3%), five cohorts for cancer (0.11, 95% CI: 0.50-0.25; I^2 = 87.1%), and five cohorts for respiratory diseases (0.09, 95%CI 0.04, 0.17; I^2 = 63.2%) (**Table 3; Figure 3)**. These deaths were elevated relative to the expected rate, particularly respiratory diseases (pooled SMR: 24.12, 95% CI 6.03, 96.43) (**Table 3, Figure 4**), although this estimate should be treated with caution being based on one cohort.

[Figure 4]

Mortality relative risks

Estimated study-level mortality RRs for all-cause and cause-specific mortality are presented in **Appendix K** and are similar to SMRs.

We conducted several additional analyses to examine our approach to imputation of data. First, we generated estimated CMRs and person years for studies that had already reported all these metrics and found reasonable consistency across these (**Appendix H**). Second, we compared pooled estimates that did not include imputed CMRs with those that did, and again found reasonable consistency (**Appendix L**). Finally, as noted earlier, we also contrasted pooled SMRs that only included author-reported SMRs with those that included our imputed SMRs (**Appendix L**); in some cases there were very few or only one cohort that had author-reported SMRs, so there are few data, but the all-cause estimates were remarkably similar. Finally, we examined the potential impact of the two very large cohorts on pooled estimates by generating pooled estimates without those two cohorts (22, 23). Pooled all-cause CMR was 1.23 per 100PY (95%CI 0.75, 2.02; I^2=98.7%; n=15 cohorts) compared to 1.24 per 100PY (95% CI: 0.86, 1.78; I^2=98.8%; n=16 cohorts) including those cohorts; pooled accidental injury CMR was 0.13 per 100PY (95%CI 0.06, 0.25; I^2 =82.5%; n=5 cohorts) compared to 0.09 per 100PY (95%CI: 0.04, 0.22; I^2=95.4%; n=6 cohorts) including those cohorts; and pooled suicide CMR was 0.08 per 100PY (95%CI 0.04, 0.15; I^2=73.0%' n=7 cohorts) compared to 0.07 per 100PY (95%CI: 0.04, 0.10; I^2=72.6%; n=8 cohorts) including those cohorts.

DISCUSSION

This review suggests that people with regular or problematic cocaine use have, on average, an excess mortality risk six times (95%CI four to nine times) the expected rate for their age-matched counterparts in the general population. The most highly elevated causes of deaths were drug-related or arising from traumatic causes (suicide, accidental injury or homicide) – all of which are preventable. Mortality was also elevated for communicable diseases (e.g., AIDS-related mortality) and other natural causes of death, including cardiovascular disease. These findings are consistent with the known effects of cocaine (6) and other risk pathways associated with these health outcomes (6). The potential for a growing population of people with regular or problematic cocaine use – coupled with the current findings of elevated mortality risk – reinforces the need for expansion of evidence-based prevention and intervention efforts to reduce health harms.

It is important to note that it is not the case that elevations in mortality necessarily reflect direct causal effects of cocaine use. In some instances elevated mortality may reflect other lifestyle factors and exposure to risk environments. But there are some causes of death for which there is good evidence of a direct causal impact. Cocaine carries a clear risk for cardiovascular events (e.g., heart attack, arrhythmia or stroke) (24). Risk of mortality can only be mitigated through reduced use. Yet, a major hurdle in reducing mortality associated with cocaine use is the lack of treatment options for cocaine dependence. There is no strong clinical evidence to support pharmacotherapies for cocaine dependence despite trials of various medicines(25-30). Psychosocial treatment (primarily contingency management) may decrease frequency of use and increase length of abstinence; longer-term impacts post-treatment are less clear (31). However, accessibility and affordability of psychosocial treatment are major issues in many countries, particularly for consumers of crack cocaine who are typically more socially marginalised relative to consumers of powder cocaine (32).

There are a range of secondary interventions that can address mortality risk pathways. Prevalence of HIV, HCV and other infectious diseases is often higher among people who use cocaine (and crack

cocaine specifically) relative to the general population (33), driving AIDS-related mortality and likely contributing to excess mortality from liver disease. Regular HIV and HCV testing coupled with access to HIV antiretroviral therapies and HCV direct-acting antiviral agents could significantly reduce HIV and HCV related mortality. Access to these services is suboptimal in almost all countries (34). Strategies to prevent transmission include provision of sterile needles and smoking pipes, free condoms, and pre-exposure prophylaxis for HIV and sexually transmitted infections (25). Rigorous evaluation of some of these interventions is yet to be undertaken (particularly with respect to their impacts on mortality) however efforts to directly engage people who smoke crack cocaine in particular are laudable as existing services targeted at people who inject drugs may not meet the needs of this group.

Whilst preventable, reducing excess mortality due to traumatic causes (e.g., suicide, homicide, and accidental injury) is challenging. People with regular or problematic cocaine use are often from socio-economically disadvantaged areas and are more likely to be exposed to environmental risk factors (e.g., violence, crime) than people who use other drugs (35). There is also a significant gap in evidence regarding interventions to reduce agitation related to stimulant intoxication and to manage violence risk more broadly amongst this group (36). Treatment for cocaine dependence thus needs to considerate of possible means for reducing the risk of injury and violent behaviour against a backdrop of broader environmental risk factors. CBT can also reduce suicide risk in substance-using populations (37).

Strengths and limitations

There has been a significant growth in the literature on mortality among people who report regular or problematic cocaine use, with 13 new cohorts identified since the previous review in 2008(8). Cohorts were recruited from regions with the highest levels of cocaine use (i.e., North America, Western Europe and Latin America; 1), with Australasia and Central Europe being notable exceptions. There are limited data on cocaine use in many of the remaining regions (e.g., Asian and African regions;

1), highlighting the challenge of capturing health harms associated with regular or problematic cocaine use in these regions.

Limitations of existing studies included uncertain representativeness of samples and poor reporting of methodological detail. Many of the cohorts included here were derived from a single sample type: typically, those individuals engaged with health services. Linkage of administrative data from healthcare services could be used in future studies. Secondly, data were often missing on how causes of death were defined and, where available, varied between studies. Although there are likely many contributors to heterogeneity in cause-specific mortality estimates, use of standardised definitions of cause-specific mortality (38) would reduce this potential source of variability. Nonetheless, it is important to acknowledge that varying definitions of causes likely contributed to heterogeneity across studies. Ideally, an approach where people used standardised definitions of causes of mortality might occur in future studies (e.g., 38), permitting some examination of whether this explains some of the variation observed.

We were thorough in searching for relevant studies, however, we may have missed eligible cohorts or made errors. Where necessary, we sought additional data from authors and we generated estimates of CMRs, SMRs and RRs where possible. There are potential biases introduced by our computation of person years where this was not reported, including impaired capacity to account for censoring, however sensitivity analyses showed relative consistency between imputed and study-reported person-years when we tested our approach on those studies which did provide the latter information. Computing SMRs and RRs was achieved by using estimates from the GDB study, the most comprehensive effort globally to estimate prevalence of cocaine dependence and of population-level cause-specific mortality (14). Pooled SMRs including estimates imputed from GBD typically fell within the confidence interval of the pooled SMRs from author-reported estimates only. We acknowledge that the GBD data may have some limitations and there was minor variability between pooled

estimates of author-reported SMRs versus author-reported and imputed SMRs. Reporting of all-cause and cause-specific SMRs in future work would improve confidence in existing estimates. Further, RRs should be treated with caution, being based on prevalence of cocaine dependence extracted from the GDB study, and likely of lower prevalence than regular and/or problematic cocaine use.

Finally, some variability in cohort definition and study design should also be noted. This was explored via meta-regression and stratified meta-analyses; although cohort definition (i.e. meeting criteria for dependence vs not) was not associated with heterogeneity in CMR/SMR, other aspects of study design (e.g., recruitment setting, sampling frame) were associated with heterogeneity in estimates.

Conclusions

There has been increased study of cohorts of people reporting regular or problematic cocaine use. For this reason, we could quantify excess mortality by cause of death in the current review. Synthesis of this evidence suggests people with regular or problematic cocaine use have, on average, six times (95%CI four to nine times) higher mortality risk than their age and sex peers in the general population. Excess mortality risk is particularly evident for traumatic causes of deaths and causes likely attributable to infectious diseases. These deaths are mostly preventable. A lack of treatment options for cocaine dependence mean current efforts rely heavily on other prevention and intervention strategies to address risk pathways to mortality.

ACKNOWLEDGEMENTS

We wish to thank the following people for provision of data: Andrea Jones, William G. Honer, Kanna Hayashi, Roberto Muga, Bruno Ledergerber, and Rainer Weber.

REFERENCES

1. UNITED NATIONS OFFICE ON DRUGS AND CRIME. World Drug Report 2019, Geneva: UNODC; 2019.
2. EUROPEAN MONITORING CENTRE FOR DRUGS AND DRUG ADDICTION. European Drug Report 2019: Trends and developments, Luxembourg: Publications Office of the European Union; 2019.
3. HATSUKAMI D. K., FISCHMAN M. W. Crack cocaine and cocaine hydrochloride: Are the differences myth or reality?, Jama 1996: 276: 1580-1588.
4. CONE E. J. Pharmacokinetics and pharmacodynamics of cocaine, Journal of analytical toxicology 1995: 19: 459-478.
5. SORDO L., INDAVE B. I., BARRIO G., DEGENHARDT L., DE LA FUENTE L., BRAVO M. J. Cocaine use and risk of stroke: A systematic review, Drug and Alcohol Dependence 2014: 142: 1-13.
6. BUTLER A. J., REHM J., FISCHER B. Health outcomes associated with crack-cocaine use: Systematic review and meta-analyses, Drug and Alcohol Dependence 2017: 180: 401-416.
7. DI COSOLA M., TURCO M., ACERO J., NAVARRO-VILA C., CORTELAZZI R. Cocaine-related syndrome and palatal reconstruction: report of a series of cases, International Journal of Oral and Maxillofacial Surgery 2007: 36: 721-727.
8. DEGENHARDT L., SINGLETON J., CALABRIA B., MCLAREN J., KERR T., MEHTA S. et al. Mortality among cocaine users: A systematic review of cohort studies, Drug and Alcohol Dependence 2011: 113: 88-95.
9. SCHOLL L., SETH P., KARIISA M., WILSON N., BALDWIN G. Drug and opioid-involved overdose deaths—United States, 2013–2017, Morbidity and Mortality Weekly Report 2019: 67: 1419.
10. OFFICE FOR NATIONAL STATISTICS. Deaths related to drug poisoning in England and Wales: 2017 registrations: Office for National Statistics; 2018.
11. MOHER D., LIBERATI A., TETZLAFF J., ALTMAN D. G. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Annals of internal medicine 2009: 151: 264-269.
12. VERITAS HEALTH INNOVATION. Covidence systematic review software. Melbourne, Australia.
13. BERO L., CHARTRES N., DIONG J., FABBRI A., GHERSI D., LAM J. O. et al. The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures, Systematic Reviews 2018: 7: 242.
14. GLOBAL BURDEN OF DISEASE 2017 CAUSES OF DEATH COLLABORATORS. Global, regional, and national age-sex specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017, The Lancet 2018: 392: 1736-1788.
15. ROTHMAN K. J., GREENLAND S., LASH T. Types of epidemiologic studies, Modern epidemiology 2nd ed: Lippincott Raven 1998: 74-75.
16. JONES M. E., SWERDLOW A. J. Bias in the standardized mortality ratio when using general population rates to estimate expected number of deaths, American journal of epidemiology 1998: 148: 1012-1017.
17. HARRIS R. J., DEEKS J. J., ALTMAN D. G., BRADBURN M. J., HARBORD R. M., STERNE J. A. Metan: fixed- and random-effects meta-analysis, The Stata Journal 2008: 8: 3-28.
18. STATACORP. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC; 2019.
19. HIGGINS J., GREEN S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 2011.
20. COHEN P., SAS A. Cocaine use in Amsterdam in non deviant subcultures, Addiction Research 1994: 2: 71-94.
21. MOLIST G., BRUGAL M. T., BARRIO G., MESIAS B., BOSQUE-PROUS M., PARES-BADELL O. et al. Effect of ageing and time since first heroin and cocaine use on mortality from external and natural causes in a Spanish cohort of drug users, International Journal of Drug Policy 2018: 53: 8-16.

22. Callaghan R. C., Gatley J. M., Veldhuizen S., Lev-Ran S., Mann R., Asbridge M. Alcohol- or drug-use disorders and motor vehicle accident mortality: a retrospective cohort study, Accident; analysis and prevention 2013: 53: 149-155.
23. Bohnert K. M., Ilgen M. A., Louzon S., McCarthy J. F., Katz I. R. Substance use disorders and the risk of suicide mortality among men and women in the US Veterans Health Administration, Addiction 2017: 112: 1193-1201.
24. Schwartz B. G., Rezkalla S., Kloner R. A. Cardiovascular effects of cocaine, Circulation 2010: 122: 2558-2569.
25. Fischer B., Blanken P., Da Silveira D., Gallassi A., Goldner E. M., Rehm J. et al. Effectiveness of secondary prevention and treatment interventions for crack-cocaine abuse: A comprehensive narrative overview of English-language studies, International Journal of Drug Policy 2015: 26: 352-363.
26. Pani P. P., Trogu E., Vecchi S., Amato L. Antidepressants for cocaine dependence and problematic cocaine use, Cochrane Database of Systematic Reviews 2011.
27. Castells X., Cunill R., Pérez-Mañá C., Vidal X., Capellà D. Psychostimulant drugs for cocaine dependence, Cochrane Database of Systematic Reviews 2016.
28. Minozzi S., Amato L., Pani P. P., Solimini R., Vecchi S., De Crescenzo F. et al. Dopamine agonists for the treatment of cocaine dependence, Cochrane Database of Systematic Reviews 2015.
29. Pani P. P., Trogu E., Vacca R., Amato L., Vecchi S., Davoli M. Disulfiram for the treatment of cocaine dependence, Cochrane Database of Systematic Reviews 2010.
30. Indave B. I., Minozzi S., Pani P. P., Amato L. Antipsychotic medications for cocaine dependence, Cochrane Database of Systematic Reviews 2016.
31. Minozzi S., Saulle R., De Crescenzo F., Amato L. Psychosocial interventions for psychostimulant misuse, Cochrane Database of Systematic Reviews 2016.
32. Palamar J. J., Davies S., Ompad D. C., Cleland C. M., Weitzman M. Powder cocaine and crack use in the United States: An examination of risk for arrest and socioeconomic disparities in use, Drug and alcohol dependence 2015: 149: 108-116.
33. DeBeck K., Kerr T., Li K., Fischer B., Buxton J., Montaner J. et al. Smoking of crack cocaine as a risk factor for HIV infection among people who use injection drugs, Cmaj 2009: 181: 585-589.
34. Larney S., Peacock A., Leung J., Colledge S., Hickman M., Vickerman P. et al. Global, regional, and country-level coverage of interventions to prevent and manage HIV and hepatitis C among people who inject drugs: a systematic review, The Lancet Global Health 2017: 5: e1208-e1220.
35. Fischer B., Rehm J., Patra J., Kalousek K., Haydon E., Tyndall M. et al. Crack across Canada: comparing crack users and crack non-users in a Canadian multi-city cohort of illicit opioid users, Addiction 2006: 101: 1760-1770.
36. Bunting P. J., Fulde G. W. O., Forster S. L. Comparison of crystalline methamphetamine ("ice") users and other patients with toxicology-related problems presenting to a hospital emergency department, The Medical journal of Australia 2007: 187: 564-566.
37. Calear A. L., Christensen H., Freeman A., Fenton K., Busby Grant J., van Spijker B. et al. A systematic review of psychosocial suicide prevention interventions for youth, Eur Child Adolesc Psychiatry 2016: 25: 467-482.
38. Randall D., Roxburgh A., Gibson A., Degenhardt L. Mortality among people who use illicit drugs: A toolkit for classifying major causes of death. NDARC Technical Report No. 301, Sydney: University of New South Wales. http://ndarc.med.unsw.edu.au/NDARCWeb.nsf/resources/TR+298-302/$file/TR+301.pdf. Accessed on February 25th 2010.; 2009.
39. Accurso A. J., Rastegar D. A., Ghazarian S. R., Fingerhood M. I. Impact of hepatitis C status on 20-year mortality of patients with substance use disorders, Addiction science & clinical practice 2015: 10: 1-8.

40. ARENDT M., MUNK-JORGENSEN P., SHER L., JENSEN S. O. W. Mortality among individuals with cannabis, cocaine, amphetamine, MDMA, and opioid use disorders: A nationwide follow-up study of Danish substance users in treatment, Drug and Alcohol Dependence 2011: 114: 134-139.
41. BARRIO G., MOLIST G., DE LA FUENTE L., FERNANDEZ F., GUITART A., BRAVO M. J. et al. Mortality in a cohort of young primary cocaine users: Controlling the effect of the riskiest drug-use behaviors, Addictive Behaviors 2013: 38: 1601-1604.
42. CALLAGHAN R. C., CUNNINGHAM J. K., VERDICHEVSKI M., SYKES J., JAFFER S. R., KISH S. J. All-cause mortality among individuals with disorders related to the use of methamphetamine: A comparative cohort study, Drug and Alcohol Dependence 2012: 125: 290-294.
43. DE LA FUENTE L., MOLIST G., ESPELT A., BARRIO G., GUITART A., BRAVO M. J. et al. Mortality risk factors and excess mortality in a cohort of cocaine users admitted to drug treatment in Spain, Journal of Substance Abuse Treatment 2014: 46: 219-226.
44. BRUGAL M., MOLIST G., SARASA-RENEDO A., DE LA FUENTE L., ESPELT A., MESIAS B. et al. Assessing gender disparities in excess mortality of heroin or cocaine users compared to the general population, International Journal of Drug Policy 2016: 38: 36-42.
45. COLELL E., DOMINGO-SALVANY A., ESPELT A., PARES-BADELL O., BRUGAL M. T. Differences in mortality in a cohort of cocaine use disorder patients with concurrent alcohol or opiates disorder, Addiction 2018: 113: 1045-1055.
46. DIAS A. C., ARAUJO M. R., DUNN J., SESSO R. C., DE CASTRO V., LARANJEIRA R. Mortality rate among crack/cocaine-dependent patients: A 12-year prospective cohort study conducted in Brazil, Journal of Substance Abuse Treatment 2011: 41: 273-278.
47. GOSSOP M., STEWART D., TREACY S., MARSDEN J. A prospective study of mortality among drug misusers during a 4-year period after seeking treatment, Addiction 2002: 97: 39-47.
48. HAYASHI K., DONG H., MARSHALL B. D., MILLOY M. J., MONTANER J. S., WOOD E. et al. Sex-Based Differences in Rates, Causes, and Predictors of Death Among Injection Drug Users in Vancouver, Canada, American journal of epidemiology 2016: 183: 544-552.
49. TYNDALL M. W., CRAIB K. J. P., CURRIE S., LI K., O'SHAUGHNESSY M. V., SCHECHTER M. T. Impact of HIV infection of mortality in a cohort of injection drug users, Journal of Acquired Immune Deficiency Syndrome 2001: 28: 351-357.
50. HSER Y. I., KAGIHARA J., HUANG D., EVANS E., MESSINA N. Mortality among substance-using mothers in California: a 10-year prospective study, Addiction 2012: 107: 215-222.
51. LOPEZ D., MARTINEAU H., PALLE C. Mortality of individuals arrested for heroin, cocaine or crack use. In: (OFDT) F. m. c. f. d. a. d. a., editor. Tendances; 2004.
52. MARKOTA M., CROARKIN P. E., BOBO W. V. Increased 5-year all-cause mortality in youth with positive urine cocaine drug screens, Journal of the American Academy of Child and Adolescent Psychiatry 2016: 55 (10 Supplement 1): S148.
53. MARTELL B. A., ORSON F. M., POLING J., MITCHELL E., ROSSEN R. D., GARDNER T. et al. Cocaine vaccine for the treatment of cocaine dependence in methadone-maintained patients: A randomized, double-blind, placebo-controlled efficacy trial, Archives of General Psychiatry 2009: 66: 1116-1123.
54. NIELSEN S. F., HJORTHOJ C. R., ERLANGSEN A., NORDENTOFT M. Psychiatric disorders and mortality among people in homeless shelters in Denmark: A nationwide register-based cohort study, The Lancet 2011: 377: 2205-2214.
55. O'DRISCOLL P. T., MCGOUGH J., HAGAN H., THIEDE H., CRITCHLOW C., ALEXANDER E. R. Predictors of accidental fatal drug overdose among a cohort of injection drug users, American Journal of Public Health 2001: 91: 984-987.
56. PAVARIN R. M., FIORITTI A. Mortality Trends among Cocaine Users Treated between 1989 and 2013 in Northern Italy: Results of a Longitudinal Study, Journal of Psychoactive Drugs 2017: 50: 72-80.

57. PAVARIN R. M. Cocaine consumption and death risk: A follow-up study on 347 cocaine addicts in the metropolitan area of Bologna, Annali-Istituto Superiore di Sanita 2008: 44: 91-98.
58. PAVARIN R. M. Mortality risk for cocaine abusers in relation to heroin use: A follow-up study, Substance Use & Misuse 2013: 48: 702-710.
59. RYB G. E., COOPER C. C., DISCHINGER P. C., KUFERA J. A., AUMAN K. M., SODERSTROM C. A. Suicides, homicides, and unintentional injury deaths after trauma center discharge: Cocaine use as a risk factor, Journal of Trauma - Injury, Infection and Critical Care 2009: 67: 490-496.
60. SANVISENS A., VALLECILLO G., BOLAO F., RIVAS I., FONSECA F., FUSTER D. et al. Temporal trends in the survival of drug and alcohol abusers according to the primary drug of admission to treatment in Spain, Drug and Alcohol Dependence 2014: 136: 115-120.
61. VAN HAASTRECHT H. J. A., VAN AMEIJDEN E. J. C., VAN DEN HOEK J. A. R., MIENTJES G. H. C., BAX J. S., COUTINHO R. A. Predictors of mortality in the Amsterdam cohort of human immunodeficiency virus (HIV)-positive and HIV-negative drug users, American journal of epidemiology 1996: 143: 380-391.
62. VLAHOV D., WANG C., OMPAD D., FULLER C. M., CACERES W., OUELLET L. et al. Mortality risk among recent-onset injection drug users in five U.S. cities, Subst Use Misuse 2008: 43: 413-428.
63. WANG C., VLAHOV D., GALAI N., COLE S. R., BARETA J., POLLINI R. et al. The effect of HIV infection on overdose mortality, AIDS 2005: 19: 935-942.

Table 1: Characteristics of included studies

Study	Country	Years conducted[a]	Sample	N people	N person years[b]
1. Accurso, 2015(39)	United States	1990-2010	People "abusing" cocaine and presenting for detoxification at Chemical Dependence Unit at John Hopkins Bayview Medical Center in Baltimore between 1990-1991	315	5780*
2. Arendt, 2011(40)	Denmark	1996-2006	People receiving publicly funded treatment for illicit substance use disorder and primarily using cocaine across Denmark between 1996-2006, identified from the Danish Substance Abuse Treatment Register	838	2571*
3. Barrio, 2013(41)	Spain	2004-2010	People who reported regular cocaine use (≥ 52 days/last year) recruited from drug scenes and non-treatment settings in Madrid, Barcelona, and Seville, Spain, between 2004-2006	714	3922
4. Bohnert, 2017(23)	United States	2006-2011	People receiving Veteran Health Administration (VHA) care in the 2005 financial year diagnosed with cocaine use disorder and still alive in 2006 as identified using VHA National Patient Care Database	83808	468560*
5. Callaghan, 2013(22) *(Callaghan, 2012(42))*	United States	1990-2005	People hospitalised with a cocaine use disorder diagnosis in California between 1990-2005 from the Patient Discharge Database	48949	395738
6. de la Fuente, 2016(43) *(Brugal, 2016(44); Colell, 2018(45); Molist, 2018(21))*	Spain	1997-2008	People starting drug treatment for cocaine use disorder in a publicly owned or funded treatment centre in Barcelona and Madrid between 1997-2007	11905	65849*
7. Dias, 2011(46)[c]	Brazil	1992-2006	People who were consecutively admitted patients to Taipas General Hospital's inpatient treatment for crack/cocaine dependence between 1992-1994	131	1182*
8. Gossop, 2002(47)[c]	United Kingdom	1995-1999	People who self-reported cocaine misuse recruited to treatment programs throughout England in 1995 as part of National Treatment Outcome Research Study (NTORS) cohort	227	926*
9. Hayashi, 2016(48) *(Tyndall, 2001(49))*	Canada	1996-2011	People who injected cocaine in the 6 months prior to enrolling in the open cohorts of Vancouver Injection Drug Users Study (VIDUS) and AIDS Care Cohort to Evaluate access to Survival Sciences (ACCESS) in Vancouver between 1996-2011	1719	11749
10. Hser, 2012(50)	United States	2002-2010	Mothers enrolled in a drug treatment program with cocaine as the primary drug of concern between 2000-2002 across California as identified through California Treatment Outcome Project (CalTOP)	511	5471*

Cocaine use and mortality

11. Lopez, 2004 (OFDT)(51)[c]	France	1992-2001	People arrested in 1992, 1993, 1996 and 1997 for cocaine/crack use/dealing as identified through database of police questioning files for use of narcotics	2212	11496
12. Markota, 2016(52)	United States	1999-2011	People aged 13-18 years old attending drug and alcohol treatment and with a positive cocaine urinary toxicology screen administered at clinical sites within Mayo Health Care System between 1999-2011	63	308*
13. Martell, 2009^(53)	United States	2003-2005	People with cocaine and opioid dependence enrolled in a randomised clinical trial for cocaine vaccine from greater New Haven between 2003-2005	114	58*
14. Nielsen, 2011(54)	Denmark	1999-2009	People diagnosed with cocaine abuse and at least one contact with a homeless shelter in Denmark between 1999-2009 as identified by the Danish Homeless Register	525	5362*
15. O'Driscoll, 2001(55)	United States	1994-1997	People who inject drugs within Seattle and King County and reported cocaine as their primary drug recruited between 1994-1996	340	931*
16. Pavarin, 2017(56) *(Pavarin, 2008(57); Pavarin, 2013(58))*	Italy	1989-2013	Individuals admitted to a public drug treatment for problems caused by primary use of cocaine in Bologna (North Italy) between 1989-2013	678	4753*
17. Ryb, 2009(59)	United States	1983-1997	People discharged from R Adams Cowley Shock Trauma Center with a positive cocaine urinary toxicology screen at admission between 1983-1995	2451	15932*
18. Sanvisens, 2014(60)	Spain	1985-2008	Patients admitted to hospital detoxification for primary cocaine abuse at one of three tertiary care facilities in Barcelona and the surrounding metropolitan area between 1985-2006	945	7155
19. van Haastrecht, 1996(61)[c]	Netherlands	1985-1993	People who are HIV+ and HIV- who self-reported injecting cocaine and were recruited in Amsterdam between 1985-1992 through "low-threshold" methadone programs and clinic workers for people who use drugs and engage in sex work.	632[d]	194
20. Vlahov, 2008(62)	United States	1997-2002	People who inject drugs with self-reported injecting of cocaine everyday recruited from five U.S. cities between 1997-1999 through community-based outreach methods and enrolled in the second Collaborative Injection Drug Users Study (CIDUS-II)	102	486
21. Wang, 2005(63)[c]	United States	1988-2005	People who inject drugs who self-reported cocaine use in the previous 6 months, recruited through community in Baltimore between 1988-1989 and 1994-1998 and enrolled in AIDS Linked to Intravenous Experience study (ALIVE)	518[#]	3727

Note. *Italics* denotes associated secondary paper for the cohort; *Person years were not reported by study but calculated using formula within **Appendix H;** ^ Denotes that the study was a randomised controlled trial (RCT); [#] Denotes that the information was provided by the authors on request; [a] Period covers the start of recruitment until the end of follow-up; [b] Person-years were rounded to nearest whole number, though exact person-years reported were used for analysis; [c] Study was included in the previous review and information differs due to additional information being provided; [d] Study does not specify proportion of cohort that uses cocaine, but provides number of deaths within those who use cocaine.

Table 2: Summary of risk of bias and quality of study reporting

	Study risk of bias		Study reporting quality				
	Entire cohort		Entire cohort[a]			Cocaine sub-cohort[a]	
	Representativeness	Outcome measurement	Cohort description (age/sex)	Completeness of data (numerator/denominator)	Cause of death definition[b]	Cohort description (age/sex)	Completeness of data (numerator/denominator)
Accurso, 2015(39)	↑	↓	↑	↓	NA	↓	↓
Arendt, 2011(40)	↓	↓	↑	↑	NA	↓	↓
Barrio, 2013(41)	↓	↓	↑	↑	↓	↑	↑
Bohnert, 2017(23)	↑	↓	↑	↓	↑	↓	↓
Callaghan, 2013(22)	↓	↓	↑	↑	↑	↑	↑
Callaghan, 2012(42)	↓	↓	↑	↓	NA	↑	↓
de la Fuente, 2016(43)	↓	↓	↑	↑	NA	↑	↓
Brugal, 2016(44)	↓	↓	↑	↑	↑	↑	↑
Colell, 2018(45)	↑	↓	↑	↑	NA	↑	↑
Molist, 2018(21)	↓	↓	↑	↑	↑	↑	↑
Dias, 2011(46)	↑	↑	↑	↓	↓	↑	↓
Gossop, 2002(47)	↑	↓	↓	↓	↑	↓	↓
Hayashi, 2016(48)	↓	↓	↑	↑	↑	↓	↓
Tyndall, 2001(49)	↓	↓	↑	↓	↑	↓	↓
Hser, 2012(50)	↓	↓	↑	↓	↓	↓	↓
Lopez, 2004 (OFDT)(51)	↑	↓	↑	↓	↓	↓	↓
Markota, 2016(52)	↓	↑	↓	↓	↓	↓	↓

Cocaine use and mortality

Martell, 2009^(53)	↑	↑	↑	↓	NA	↑	↓
Nielsen, 2011(54)	↓	↓	↑	↓	↑	↓	↓
O'Driscoll, 2001(55)	↓	↓	↑	↑	↓	↓	↑
Pavarin, 2017(56)	↑	↓	↑	↓	↓	↑	↓
Pavarin, 2008(57)	↑	↓	↑	↑	↑	↑	↑
Pavarin, 2013(58)	↑	↓	↑	↓	↓	↑	↓
Ryb, 2009(59)	↑	↓	↑	↓	↓	↑	↓
Sanvisens, 2014(60)	↑	↓	↑	↑	↑	↑	↑
van Haastrecht, 1996(61)	↓	↓	↓	↑	↓	↓	↑
Vlahov, 2008(62)	↓	↓	↑	↑	NA	↓	↓
Wang, 2005(63)	↓	↓	↑	↑	↓	↓	↓
Higher risk of bias/ Lower quality of reporting[c]	9/21 (42.9%)	3/21 (14.9%)	3/21 (14.9%)	11/21 (52.4%)	10/17 (58.8%)	13/21 (61.9%)	16/21 (76.2%)

Note. Full details of the risk of bias and quality of study reporting assessment are available in **Appendix H**, noting that studies with insufficient information to evaluate each criteria were deemed 'higher risk of bias'/'lower quality of reporting'; ↓ denotes lower risk of bias or lower quality of reporting; ↑ denotes higher risk of bias or higher quality of reporting[a] 'Entire cohort' refers to reporting for sample of interest in the original study which may include people who do not consume cocaine; 'cocaine sub-cohort' refers to reporting where mortality outcomes were reported for the subsample of interest for this paper (i.e., people with regular/problematic cocaine use) but whom may not be the primary focus of the paper. [b] Includes 17 cohorts with cause-specific mortality data; 'NA' denotes cohorts where cause-specific mortality data were not collected; [c] Totals only include the primary publication if there are multiple publications reporting on the same cohort.

Table 3: Pooled all-cause and cause-specific CMRs and SMRs for people with regular/problematic cocaine use, stratified by sex, age, drug use characteristics and region

	Crude mortality rate					Standardised mortality ratio				
	N cohorts	**N people**	**Pooled crude mortality rate per 100PY (95%CI)**	**I^2**	**References**	**N cohorts (N author-reported SMR)[e]**	**N people**	**Pooled standardised mortality ratio (95%CI)**	**I^2**	**References**
All-cause mortality										
Overall	16	69,954[a]	1.24 (0.86-1.78)	98.8%	(22, 39-41, 43, 46, 48, 51, 52, 54-56, 60-63)	16 (6)	69,932[a]	6.13 (4.15-9.05)	99.0%	(39-43, 46, 48, 51, 52, 54-56, 60-63)
Sex										
Women	6	25,217[b]	0.66 (0.54-0.81)	55.6%	(22, 40, 43, 52, 54, 58)	6 (3)	25,202[b,c]	4.59 (2.68-7.87)	94.2%	(40, 42, 43, 52, 54, 57)
Men	6	37,041[b]	0.89 (0.50-1.56)	98.3%	(22, 40, 43, 52, 54, 58)	6 (4)	37,056[b]	3.42 (2.86-4.10)	77.5%	(40, 42, 43, 52, 54, 57)
Age										
< 30	2	3,677	0.67 (0.16-2.89)	97.1%	(21, 46)	2 (1)	3,677	7.75 (5.67-10.58)	0.0%	(21, 46)
≥ 30	3	8,358	1.01 (0.49-2.09)	81.5%	(21, 46, 57)	3 (1)	8,358	3.09 (1.77-5.37)	69.4%	(21, 46, 57)
Lifetime cocaine injection	5	2,679[a]	3.60 (3.32-3.90)	88.4%	(48, 55, 61-63)	5 (0)	2,679[a]	13.74 (12.67-14.90)	91.2%	(48, 55, 61-63)
Cocaine dependence/use disorder	8	64,286	1.09 (1.07-1.13)	98.4%	(22, 39, 40, 43, 46, 54, 56, 60)	8 (5)	64,286	3.24 (3.15-3.33)	97.6%	(22, 39, 40, 43, 46, 54, 56, 60)
GBD region*										
High-Income North America	7	52,006	1.56 (0.83-2.95)	99.2%	(22, 39, 48, 52, 55, 62, 63)	7 (1)	51,984	5.13 (2.34-11.25)	99.5%	(39, 42, 48, 52, 55, 62, 63)
Western Europe	8	17,817[a]	0.93 (0.49-1.78)	98.6%	(40, 41, 43, 51, 54, 56, 60, 61)	8 (4)	17,817[a]	6.01 (4.16-8.68)	94.6%	(40, 41, 43, 51, 54, 56, 60, 61)
Tropical Latin America	1	131	2.28 (1.57-3.33)	-	(46)	1 (1)	131	14.75 (9.92-21.17)	-	(46)
Cause-specific mortality										
Drug-related[c]	8	16,857	0.34 (0.10-1.15)	98.6%	(41, 44, 46, 47, 49, 55, 56, 63)	8 (2)	[c]	[c]	[c]	[c]
Suicide	8	100,854	0.07 (0.04-0.10)	72.6%	(21, 23, 41, 49, 52, 56, 59, 63)	8 (2)	100,854	6.26 (2.84-13.80)	94.4%	(21, 22, 46, 52, 56, 59)
Accidental injury	6	64,177	0.09 (0.04-0.22)	95.4%	(21, 22, 46, 52, 56, 59)	6 (3)	64,177	6.36 (4.18-9.68)	71.9%	(21, 42, 46, 52, 56, 59)
Cardiovascular disease	4	14,085	0.13 (0.07-0.24)	77.3%	(21, 49, 60, 63)	4 (1)	14,085	1.83 (0.39-8.57)	96.7%	(21, 49, 60, 63)
Homicide	3	14,487	0.09 (0.01-0.54)	98.4%	(21, 46, 59)	3 (1)	14,487	9.38 (3.45-25.48)	90.1%	(21, 46, 59)

AIDS-related	7	7,293	0.28 (0.12-0.63)	95.1%	(41, 45, 46, 49, 56, 60, 63)	6 (1)	6,576	23.12 (11.30-47.31)[g]	90.1%	(41, 45, 46, 56, 60, 63)
Cancer	5	14,763	0.11 (0.05-0.25)	87.1%	(21, 49, 56, 60, 63)	5 (2)	14,763	1.49 (0.70-3.16)	85.5%	(21, 49, 56, 60, 63)
Respiratory disease	5	6,217	0.09 (0.04-0.17)	63.2%	(41, 45, 49, 56, 63)	1 (1)[f]	852	24.12 (6.03-96.43)	-	(56)
Digestive diseases	3	13,140	0.14 (0.03-0.73)	96.1%	(21, 49, 63)	1 (1)[f]	11,905	1.90 (1.20-2.89)	-	(21)
Liver-related[d]	3	4,666	0.06 (0.01-0.55)	99.9%	(45, 46, 60)	3 (0)	4,666	3.36 (0.51-22.10)	92.5%	(45, 46, 60)

Note.

* Regions are defined as per the Global Burden of Disease (GBD) project. No studies were found for the following GBD regions: Central Asia, Central Europe, Eastern Europe, Australasia, High-Income Asia Pacific, Southern Latin America, Andean Latin America, Caribbean, Central Latin America, North Africa & Middle East, South Asia, East Asia, Oceania, Southeast Asia, Central Sub-Saharan Africa, Eastern Sub-Saharan Africa, Southern Sub-Saharan Africa or Western Sub-Saharan Africa.

[a] Except for van Haastrecht,1996(61), all studies reported the N of people who reported regular/problematic cocaine use.

[b] Except for Arendt, 2011(40), all studies reported the N of people who reported regular/problematic cocaine use.

[c] Though study estimates were available for SMR, these were deemed unstable and therefore not included. See **Appendix L** for the pooled estimate using author reported SMRs. It should be noted that drug poisoning deaths, for some studies, could include poisoning due to any drug and mental and behavioural disorders due to psychoactive substance use and other causes deemed by the authors to be drug-related (see Appendix J for ICD codes where reported).

[d] There is partial overlap with digestive diseases deaths, but liver-related deaths includes those that were specified identified as liver related whereas digestive diseases deaths included any deaths within a broader definition encompassing the digestive system (i.e., Chapter 10 of ICD-10 codes).

[e] The number in brackets denotes the number of cohorts where SMRs were reported by the authors, noting we imputed SMRs for those cohorts where these data were not reported (see Appendix L for pooled estimates using only author-reported SMRs.

[f] Due to the nature of GBD classifications, expected number of deaths was unable to be estimated resulting in no imputed SMRs to be calculated.

[g] Tyndall, 2001(49) excluded as estimate was not logical.

Table 4: Meta-regression of potential sources of heterogeneity in the pooled all-cause crude mortality rate (CMR) and standardised mortality ratio (SMR)

	Crude mortality rate				Standardised mortality ratio			
	N studies	**Coefficient (SE)**	**Adj. R^2**	***P***	**N studies**	**Coefficient (SE)**	**Adj. R^2**	***P***
Sample characteristics at baseline								
% Women	9	0.194 (0.543)	- 9.76%	0.576	**9**	**0.038 (0.051)**	**39.96%**	**0.045**
% Injecting	**8**	**5.871 (3.272)**	**68.62%**	**0.019**	8	3.091 (2.472)	17.35%	0.208
Type of cocaine use			- 1.54%				3.19%	
Cocaine/Cocaine and crack cocaine	16	ref			16	ref		
Speedball/Cocaine and Heroin	6	1.383 (0.546)		0.422	2	2.113 (1.400)		0.276
Geographic region			1.20%				- 7.77%	
% Western Europe	8	ref			8	ref		
% High-Income North America	7	1.689 (0.755)		0.262	7	- 0.207 (0.494)		0.682
% Tropical Latin America	1	2.447 (2.199)		0.337	1	0.844 (0.995)		0.412
Study characteristics								
Year of final follow-up	16	0.939 (0.034)	12.54%	0.103	16	0.925 (0.035)	16.88%	0.056
Sample size	15	1.000 (< 0.001)	- 7.82%	0.797	15	1.000 (< 0.001)	0.29%	0.345
Person years	16	1.014 (0.038)	- 6.45%	0.713	16	0.973 (0.038)	- 4.64%	0.502
Recruitment setting			-14.62%				20.51%	
Treatment clinics and other health services	6	ref			6	ref		
Hospital	3	0.750 (0.492)		0.664	**3**	**0.247 (0.146)**		**0.034**
Other	7	0.961 (0.489)		0.939	7	0.587 (0.268)		0.264
Sampling frame			34.92%				24.65%	
National/sub-national	9	ref			9	ref		
City	**7**	**2.776 (0.985)**		**0.012**	**7**	**2.579 (1.042)**		**0.034**

Note. Regions are defined as per the Global Burden of Disease (GBD) project. No studies were found for the following GBD regions: Central Asia, Central Europe, Eastern Europe, Australasia, High-Income Asia Pacific, Southern Latin America, Andean Latin America, Caribbean, Central Latin America, North Africa & Middle East, South Asia, East Asia, Oceania, Southeast Asia, Central Sub-Saharan Africa, Eastern Sub-Saharan Africa, Southern Sub-Saharan Africa or Western Sub-Saharan Africa. Ref: reference category; SE: standard error

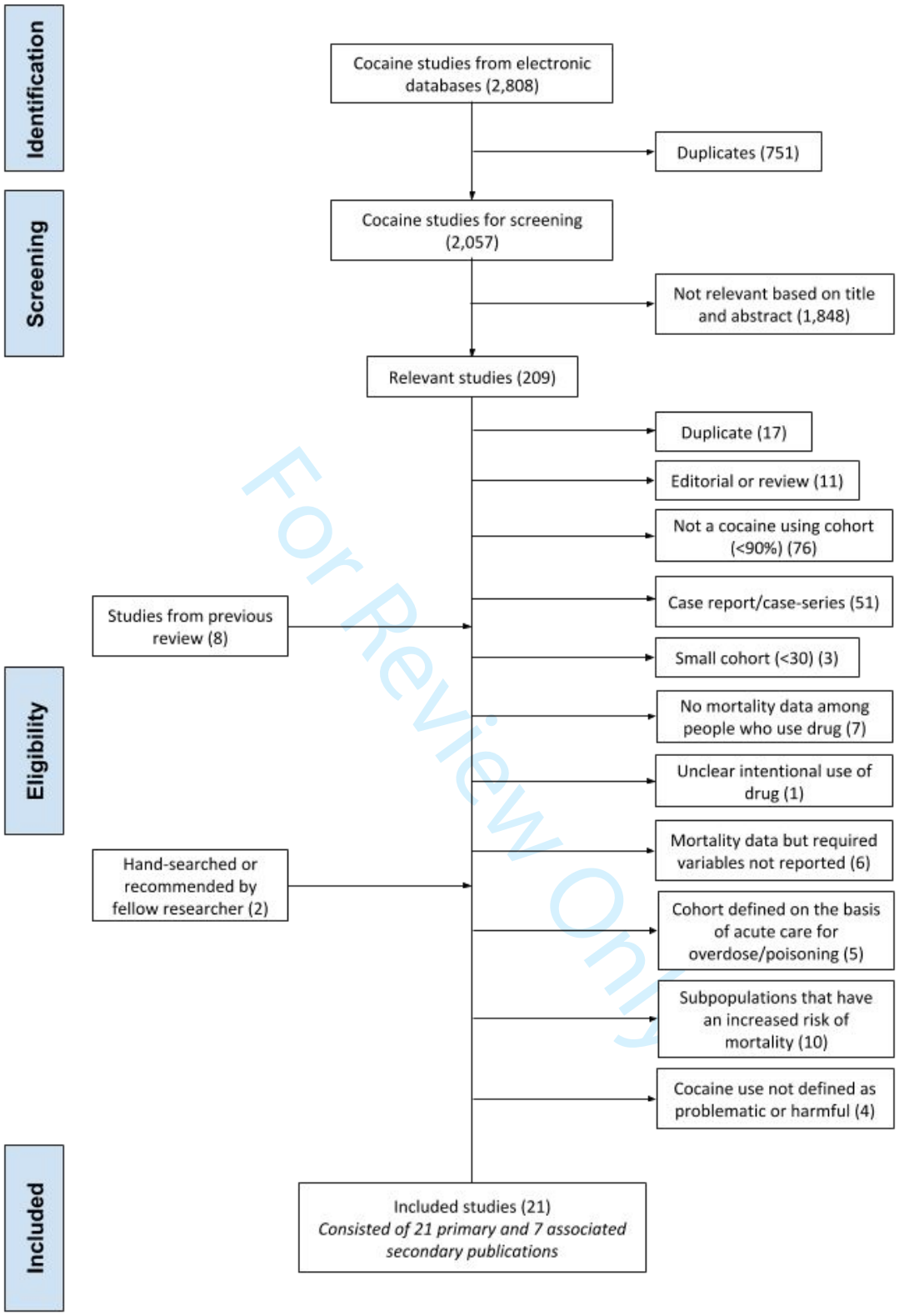
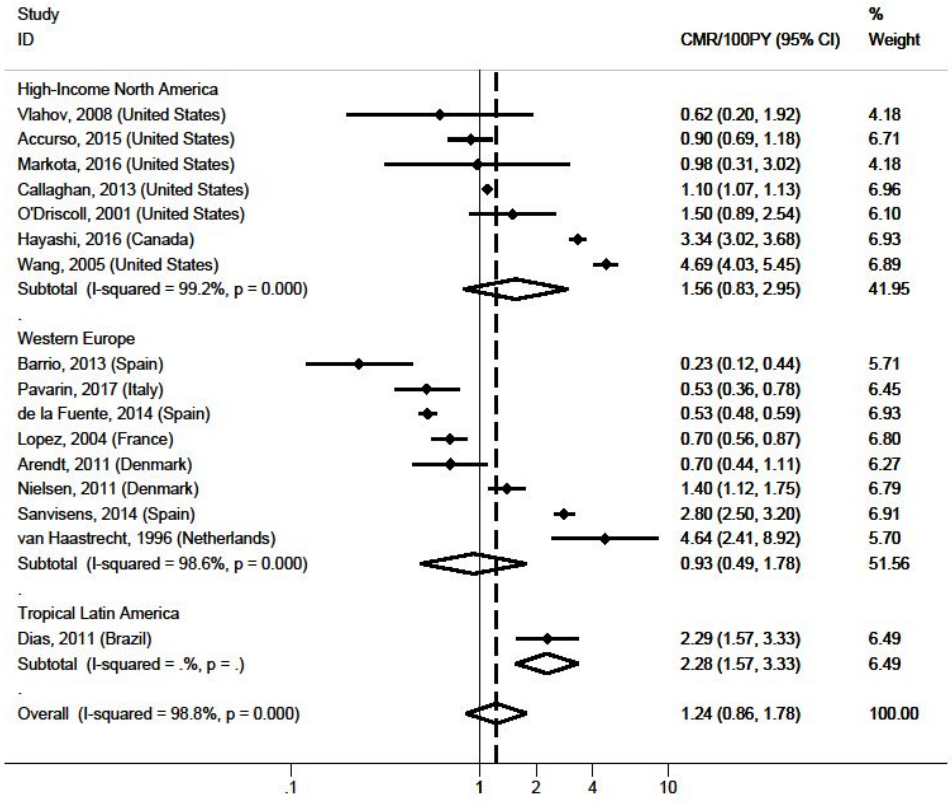
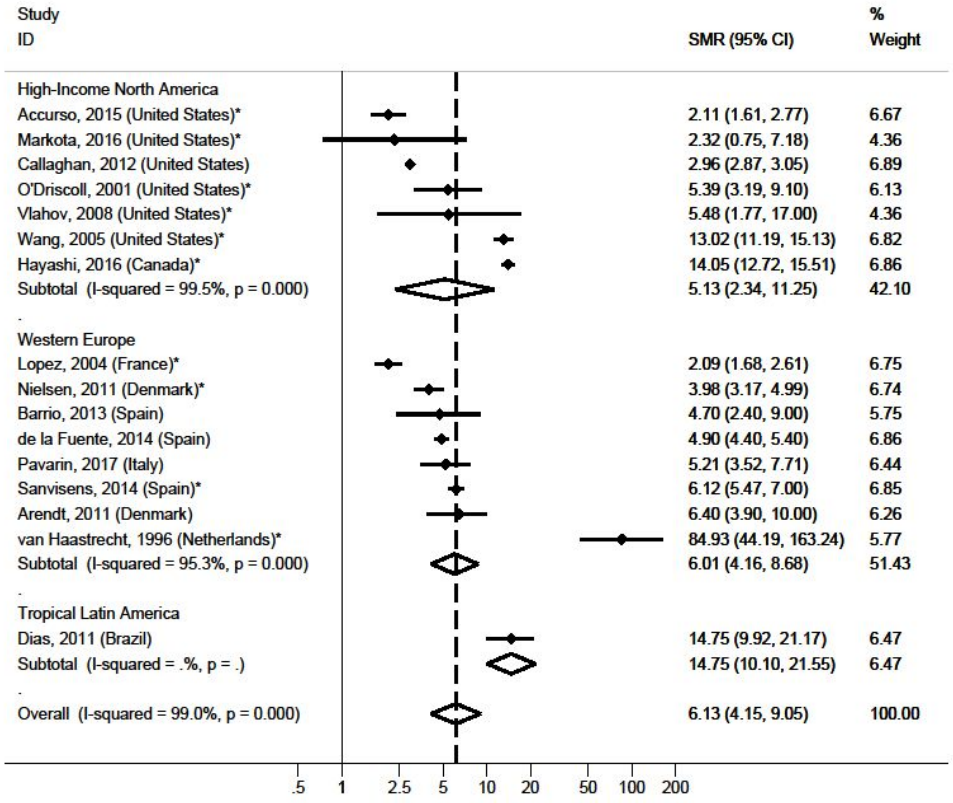


Figure 1. PRISMA flow diagram of studies reporting on mortality among people with regular or problematic cocaine use

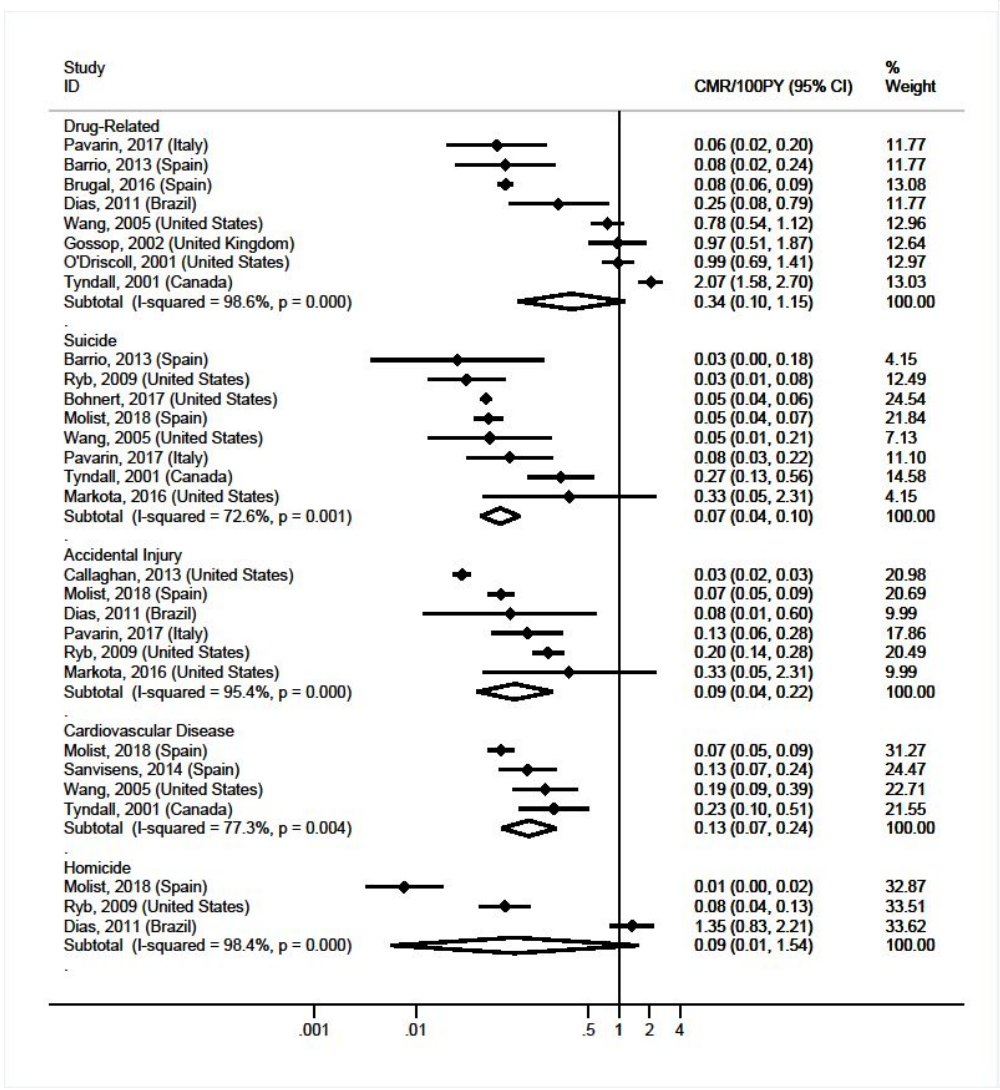
Figure 1. Pooled estimates of all-cause crude mortality rates (CMR) per 100 person-years (left) and standardised mortality ratio (SMR) (right) among people with regular or problematic cocaine use, overall and by region





Cocaine use and mortality

Figure 3: Pooled estimates of cause-specific crude mortality rates (CMR) per 100 person-years (left) and standardised mortality ratio (SMR) (right) among people with regular or problematic cocaine use



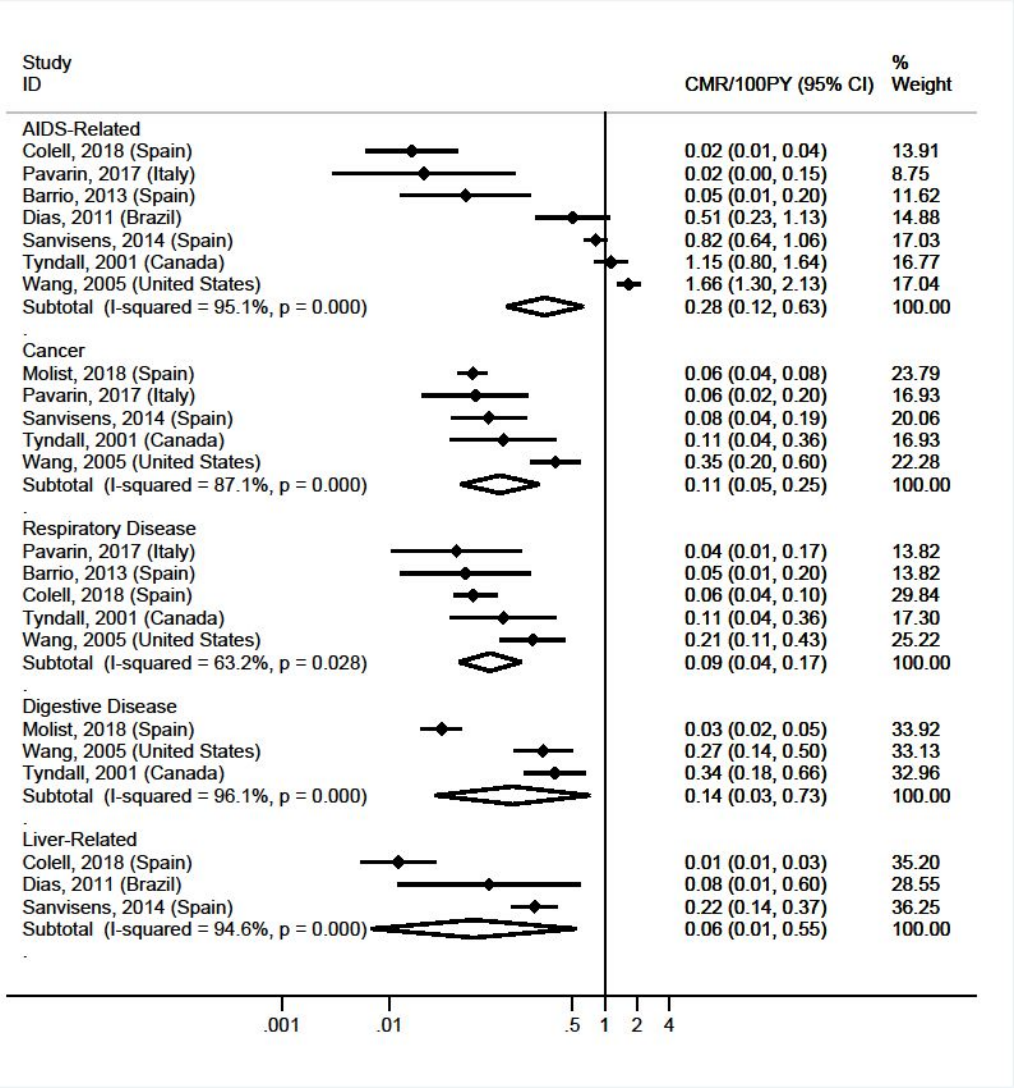
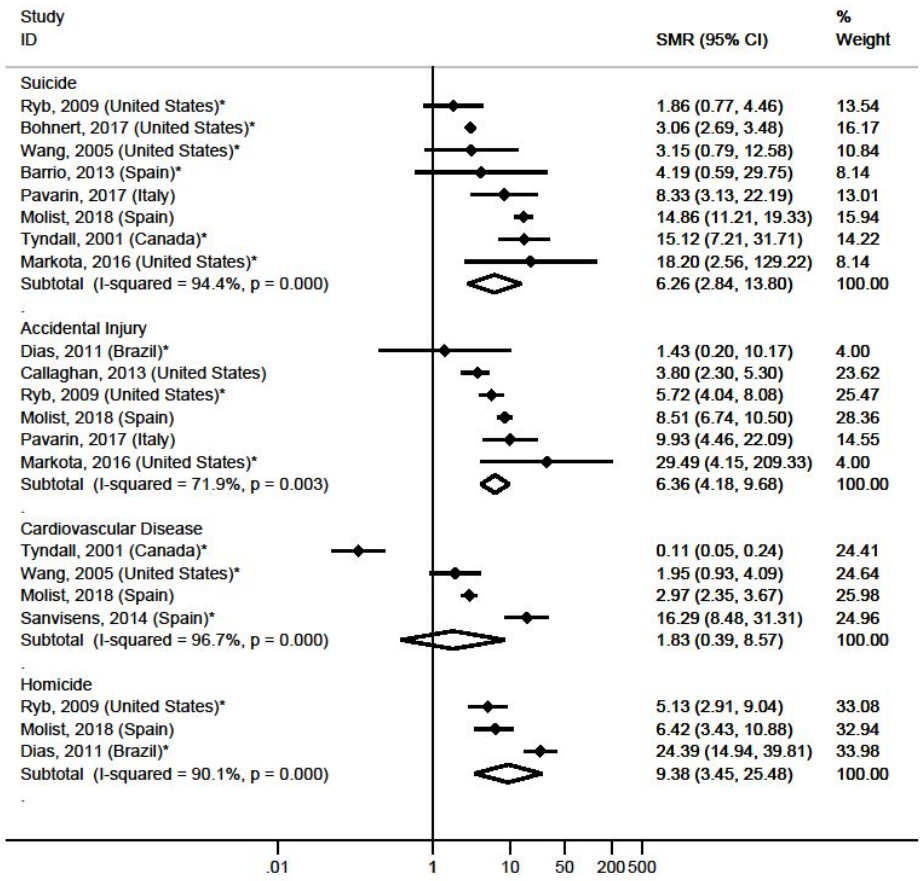
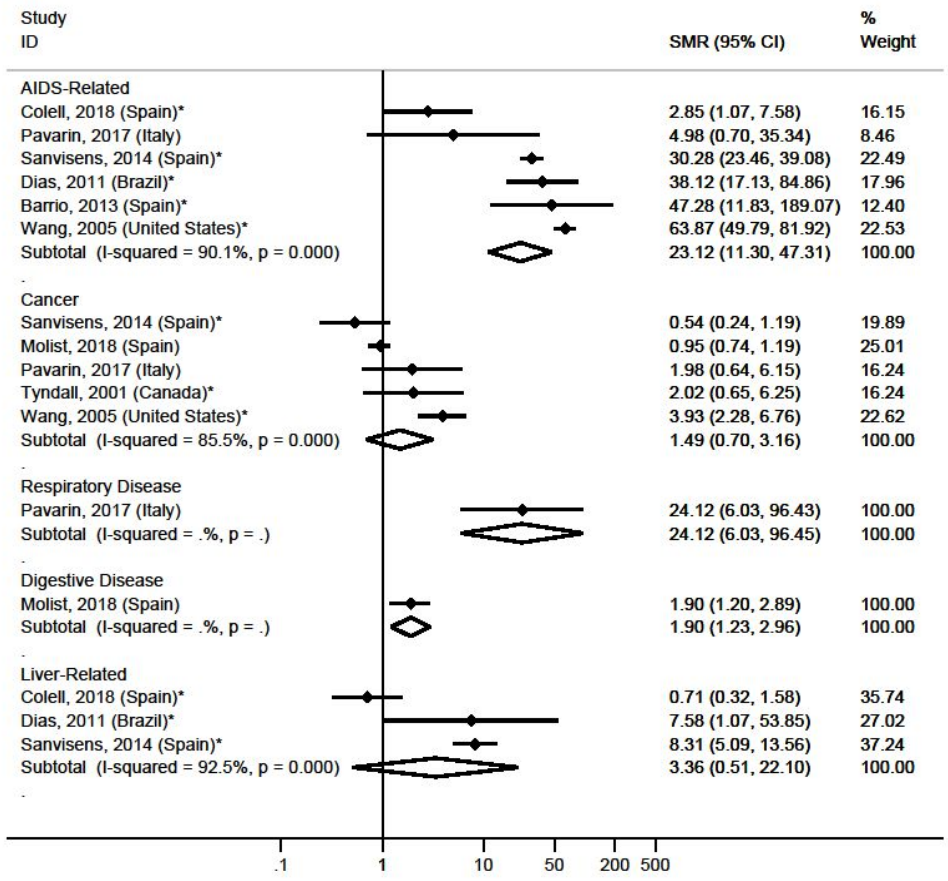


Figure 4: Pooled estimates of cause-specific standardised mortality ratio (SMR) (right) among people with regular or problematic cocaine use





* Imputed SMR was calculated for the study

Webappendices

"All-cause and cause-specific mortality among people with regular or problematic cocaine use: A systematic review and meta-analysis"

CONTENTS

Appendix A: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7; Appendix B p.6-7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8; Appendix E pp. 10-11
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7; Appendix C p. 9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix D p. 9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9-10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9; Appendix G pp. 15-16
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9-10

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10
Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9; Appendix J
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1; Appendix J
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12-16; Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2-3; Appendix J
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	16-23; Table 3; Figure 2-3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 4
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	24-25
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	25-26
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	27
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	28

Appendix B: Description of methods in PROSPERO (ID: CRD42018094623)

The aim of this project will be an update of global reviews of available data on all-cause and cause-specific mortality among people who use cocaine. The previous reviews include studies published from 1980 until 2008 new searches will be undertaken to include studies published from 2009 to current.

The Medline, Embase and PsycINFO peer-reviewed literature databases will be searched using the OVID™ interface/platform for relevant articles published from the time-periods 2009 till current. Articles of interest comprise those likely to contain data describing all-cause and cause-specific crude mortality rates (CMR) and/or standardised mortality ratios (SMR) among people who use cocaine. Sets of search strings incorporating both keywords and Medical Subject Headings (MeSH terms) reflecting drug type and mortality epidemiology from the previous reviews will be revised and expanded for this updated search. Searches will be limited to human literature. No other restrictions will be applied to the search; citations for papers in languages other than English will be included and read via Google Translate. Citations from these searches will be imported into an Endnote™ library, and duplicate citations removed.

To check for missing peer-review literature, reference lists for relevant systematic reviews identified in the peer-review literature search will be hand searched for additional papers not already identified. A final list of included studies will be distributed to experts to check if any relevant studies are missed.

Each set of search results (title and abstract) will first be screened by one team member in Covidence. All papers marked as excluded will be reviewed by a second person to ensure accuracy in first-pass screening. Each study for full-text screening will be reviewed in full by two people. Conflicts will be resolved through discussion and referral to a third party if needed.

Data will be independently extracted into an Excel worksheet template by one member of the research team and checked by a second member of the team. Bibliographic information will be extracted in addition to study specific information. Data entry will be standardized by use of a manual, which contains data entry rules. Where data are incomplete, authors will be contacted via email to obtain additional information.

Variables extracted will include study information and sample information (treatment status, HIV status, sex, percentage of sample injecting, treatment engagement). Crude mortality rates (CMRs) and standardized mortality ratios (SMRs) will be extracted as mortality measures. Cause of death information will be extracted for AIDS, overdose, suicide, traumatic (accident, homicide, injury, violence and poisoning), disease-related deaths, and other key categories. Disease-related deaths will be recoded according to the following categories; cardiovascular (endocarditis, myocardial infarction, circulatory system disease and cardiovascular disease), cerebrovascular, respiratory (pneumonia and chronic respiratory disease), liver (cirrhosis, viral hepatitis and liver disease), cancer (neoplasm, tumour and carcinoma), digestive (digestive system disease, nephritis and haemorrhage from duodenal ulcer), nervous system disease and other diseases (tuberculosis, bacterial infection, unspecified ‘other disease’ or ‘natural causes’ and when disease categories are not separated).

The quality index used in the previous reviews will be adopted for consistency. The quality index assesses each study on nine individual criteria: case ascertainment, measurement, diagnosis, estimate, numerator and denominator, data catchment, completeness, representativeness and age/sex variables. Each criterion will include a rating scale and the individual scores tallied to provide

an overall quality score. Study information necessary for quality assessment will be extracted to the Excel template. The greater the quality score, the higher the methodological quality of the study. Mortality estimates from higher rating studies may be given additional weighting in the calculation of final estimates. Quality estimates may also be used to undertake sensitivity analyses.
Crude mortality rates will be calculated as per 100 person-years. Where person-years are not reported nor made available by the authors, an approximate person-year of follow-up will be calculated, with the assumption that deaths occurred halfway through the follow-up period, so that each case contributes half the person-year follow-up of survivors.

Estimates will be analysed in subgroups according to population type (for example, estimates from cohorts recruited on the basis of having a chronic physical health condition associated with a high mortality rate may be considered separately). Random-effects meta-analyses to determine pooled all-cause and cause-specific CMR and SMR estimates will be performed using STATA. This approach uses inverse variance weighting to calculate: fixed- and random effects pooled summary estimates; confidence limits; a test for differences between study effects; and an estimate of between-study variance. The random effects model allows for heterogeneity between as well as within studies; expecting high levels of heterogeneity between cohorts, the random-effects model will be used in all meta-analyses, with confirmation through the heterogeneity c2 and I-squared statistic. To investigate the source of this heterogeneity in an attempt to reduce it, cohorts may be divided into subsamples (e.g., by sex, age group, treatment status and HIV status) and/or these factors studied as possible risk factors for mortality via meta-regression in Stata.

Appendix C: Description of databases used

Database	Information
Medline	Compiled by the U.S. National Library of Medicine (NLM) and published on the Web by Community of Science, MEDLINE® is the world's most comprehensive source of life sciences and biomedical bibliographic information. It contains nearly eleven million records from over 7,300 different publications from 1965 to November 16, 2005. *(Source: http://medline.cos.com/docs/abmedl.shtml)*
EMBASE	EMBASE is a biomedical and pharmacological database. The EMBASE journal collection is international with over 5,000 biomedical journals from 70 countries. EMBASE contains over 11 million records from 1974 to present. EMBASE features comprehensive coverage of: • Drug Research, Pharmacology, Pharmacy, Pharmacoeconomics, Pharmaceutics and Toxicology • Human Medicine (Clinical and Experimental) • Basic Biological Research • Health Policy and Management • Public, Occupational and Environmental Health • Substance Dependence and Abuse • Psychiatry • Forensic Science • Biomedical Engineering and Instrumentation *(Source: http://www.elsevier.com/wps/find/bibliographicdatabasedescription.cws_home/523328/description#description)*
PsychINFO	PsycINFO is an abstract database of psychological literature from the 1800s to the present. More than 2.4 million records as of January 2008, including journals, books and dissertations. Over 2150 journal titles covered, 98% peer-reviewed; aso books and dissertations. *(Source: http://www.apa.org/psycinfo/)*

Appendix D: Search strings and number of results for electronic literature searches

Database	Search group	Search terms
Medline*	Cocaine	Cocaine **exp Cocaine/ or exp Crack Cocaine/ or exp Cocaine-Related Disorders/ or exp Cocaine Smoking/**
	Mortality	Mortal$ or fatal$ or death$ **exp DEATH/ or exp "CAUSE OF DEATH"/ or exp DEATH, SUDDEN/ or exp Fatal Outcome/ or exp Mortality/**
EMBASE#	Cocaine	Cocaine **exp Cocaine/ or exp Cocaine Dependence/ or exp Cocaine Derivative/**
	Mortality	Mortal* or fatal* or death* **exp DEATH/ or exp "CAUSE OF DEATH"/ or exp ACCIDENTAL DEATH/ or exp SUDDEN DEATH/ or exp Fatality/ or exp Mortality/**
PsychINFO^	Cocaine	Cocaine **exp Cocaine/ or exp Crack Cocaine/**
	Mortality	Mortal* or fatal* or death* **exp "DEATH AND DYING"/ or exp Mortality/ or exp Mortality Rate**

* 'key-words' in lowercase, 'MeSH' terms in **bold** # 'key-words' in lowercase, 'EMTREE' terms in **bold**

^ 'key words' in lowercase, explode terms in **bold**

	Search terms		Database		
			EMBASE	Medline	PsycINFO
1.	Cocaine	+mortality	1980	600	228

Appendix E: Inclusion and exclusion criteria for studies

Inclusion criteria for the study population comprised:

- Cohort studies of people using cocaine (where ≥90% of the sample report use of the substance of interest; people may report using multiple drugs);
- Cohort studies that are based on a sub-group of people who use cocaine (e.g. people who use cocaine who are incarcerated).
- Cohort studies that are not based on drug use (e.g. a cohort of homeless people), but a cocaine-using sub-group is identified, and results are presented separately for this sub-group.
- Case-control studies where cases are defined by cocaine use and mortality is reported for cases and controls separately
- Clinical trials of interventions to treat cocaine use disorder (randomised controlled trials; non-randomised trials) where mortality may be reported at follow-up. Interventions may include pharmacotherapies or non-pharmacological treatments
- Secondary publications of an included cohort where the outcomes are not mortality (these may be used to assess risk of bias or to extract other baseline/demographic data not reported in the primary publication).

Inclusion criteria for the study outcome comprised of:

- Reporting raw mortality data (all-cause or cause-specific) or studies where such data can be obtained via contacting study authors.

Exclusion criteria comprised of:

- Cohort studies with a sample of less than 30 participants.
- Case reports/case series of drug-related deaths.
- Works that do not present original data (e.g. letters to the editor, editorials, commentaries)
- Works that do not present mortality data and where data could not be obtained via contacting study authors.
- Systematic reviews (although identified relevant reviews were handsearched for relevant studies which will be assessed independently against the inclusion/exclusion criteria)
- Studies where use of cocaine and mortality are not reported for the same sample of people
- Studies where it is unclear that everyone in the cohort reported intentional use of cocaine.
- Clinical trials of interventions for non-substance use disorders that are within a cocaine cohort e.g. clinical trials of HCV medicines in a cocaine cohort.

- Studies where the cohort was defined on the basis of acute care for overdose/poisoning.
- Studies where the cohort was defined by a population that has increased risk of mortality (e.g., severe health presentations or conditions, cardiovascular presentations related to cocaine exposure and being HIV positive)
- Studies where cohort reports cocaine use but it is not defined as regular or problematic.

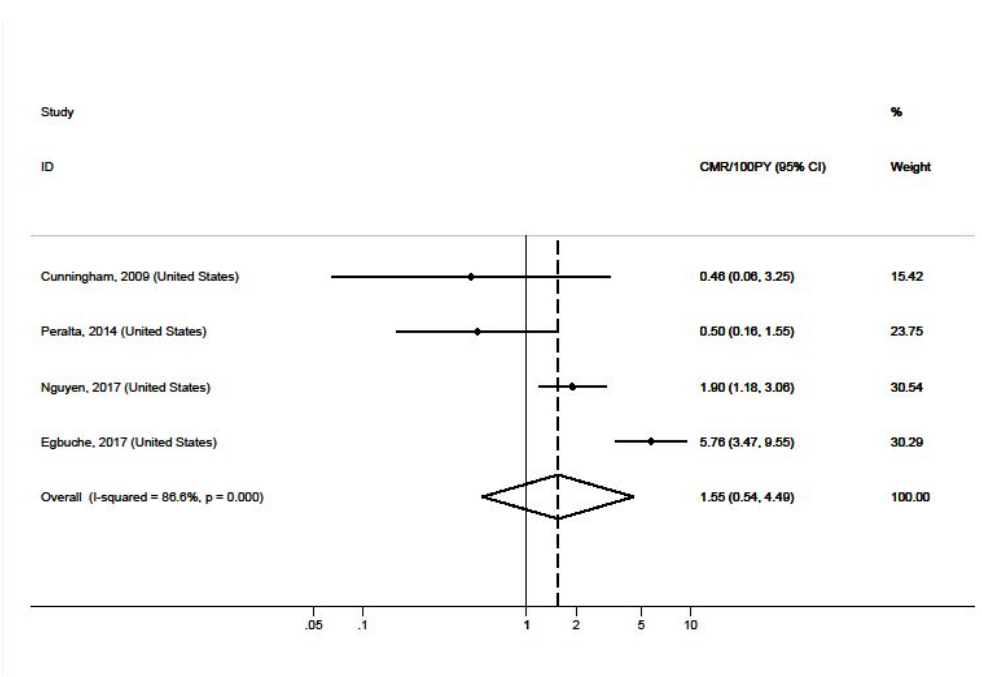
Appendix F: Cohort studies not included in main analyses

Table F1. List of identified cohort subpopulations not included in the main analyses (n=7)

Study	Country	Years conducted	Sample	N	Person years follow up	% women	Age at baseline	% PWID
1. Cunningham, 2009[1]	United States	2002-2005	People who presented for cocaine-induced chest pains, identified through a positive cocaine urine screen, to the Hurley Medical Center between 2002-2004 and followed for 1 year	219	218.5*	35%		
2. Egbuche, 2017[2]	United States	2011-2014	People with heart failure presenting to Grady Memorial Hospital, Atlanta with a positive cocaine urine toxicology test between 2011-2014	268	260.5*	24.25%	54 (mean)	
3. Nguyen, 2017[3]	United States	1993-2012	People hospitalised for acute decompensated heart failure at Michael E. DeBakey Veterans Affairs Medical Center, Houston between 1993-2012 with ICD coding of cocaine use and positive cocaine urine toxicology screen	90	892.539*	1.1%	55.5	
4. Peralta, 2014^[4]	United States	NR	People with cocaine-induced chest pain randomised to either coronary computed tomographic angiography or standard of care protocol	202	601.5*			
5. Campa, 2016[5]	United States	NR	People with HIV from the Miami Adult Studies on HIV (MASH) cohort who self-reported cocaine use and/or had a positive cocaine urine toxicology screen	156	670.8*	31%	46.4	
6. Nacher, 2009[6]	French Guiana	1996-2007	People with HIV admitted to Cayenne, Kourou, and Saint Laurent du Maroni Hospitals with crack cocaine dependence between 1996-2007 in French Hospital Database for HIV	76				
7. Weber, 2015[7]	Switzerland	2007-2013	People with HIV registered prior to April 2007 treated at outpatient clinics at five university hospitals and two large district hospitals and who self-reported cocaine use	947[#]	4531.4*			32.73%

Note. *PYFU were not reported by study but calculated using formula within **Appendix E;** ^ denotes that the study was a randomised controlled trial (RCT); NR denotes that variable was not reported by the study; [#] denotes that the information was additionally provided by authors

Figure F1. Forest plots displaying the pooled all-cause CMR per 100 person-years (left) and all-cause SMR (right) with studies containing cohorts based on cardiovascular presentations.



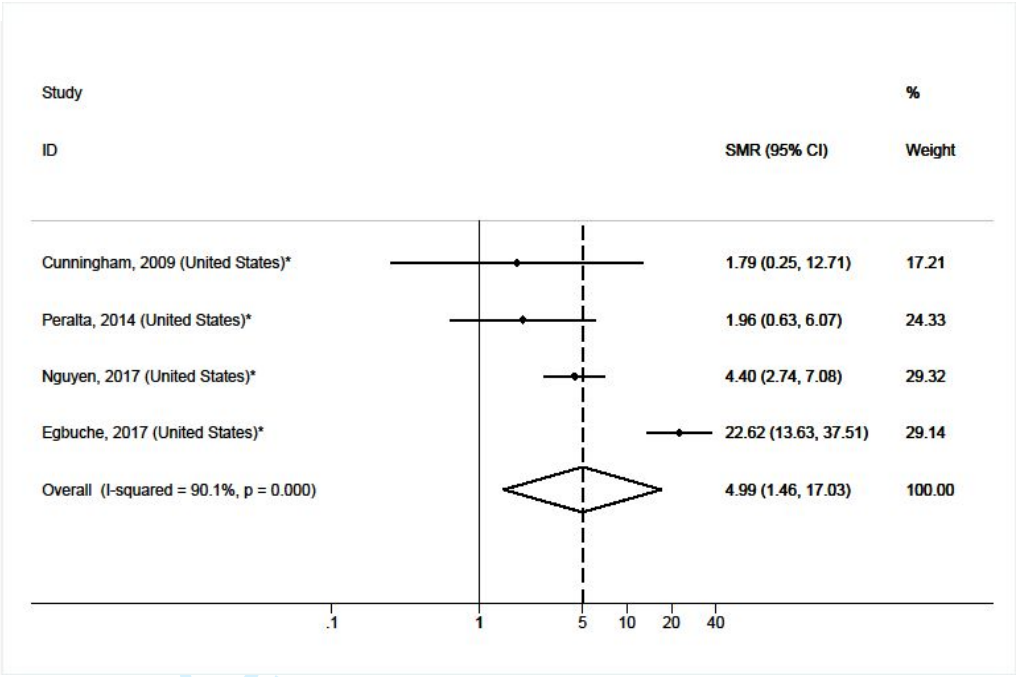
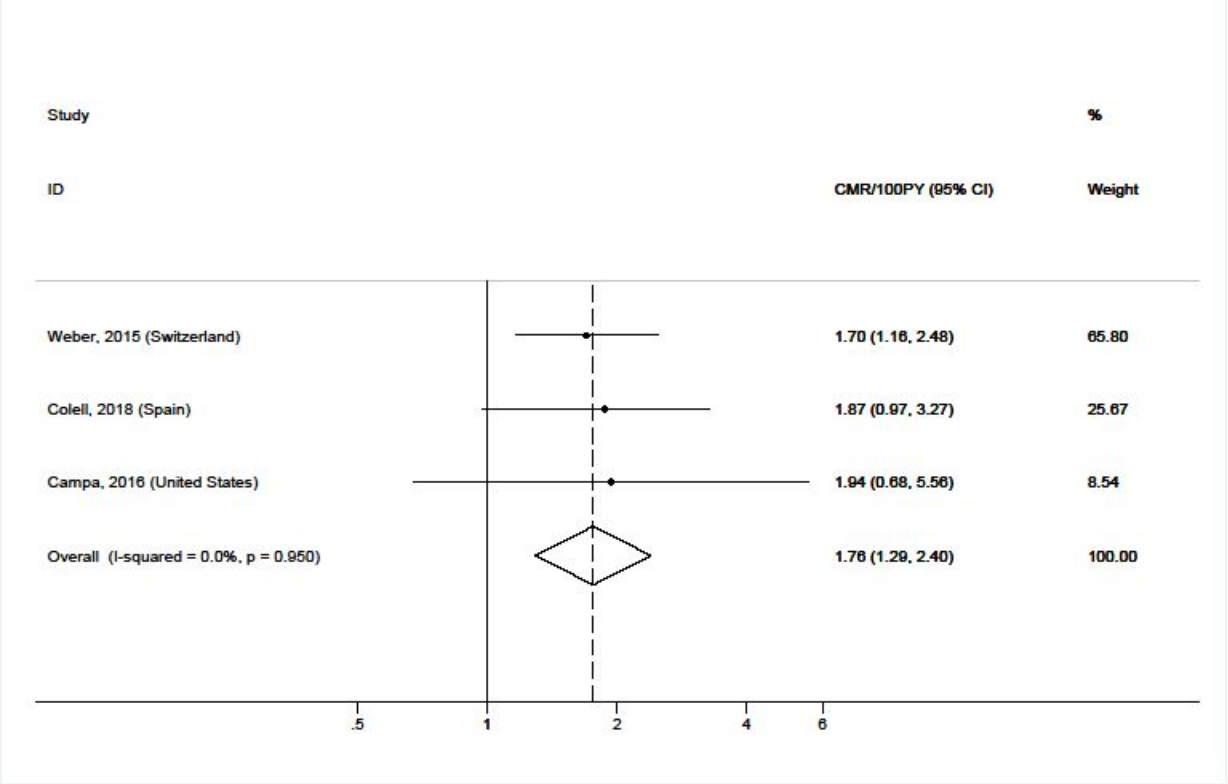


Figure F2. Forest plot displaying the pooled all-cause CMR per 100 person-years with studies that reported HIV positive subgroups.



Appendix G: Quality of reporting and risk of bias assessment tool

RISK OF BIAS DOMAINS			
	Description	**Options**	**Rating**
Representativeness[a]	How representative of the population are the cohort?	One sample type, one location One sample type, multiple locations Multiple sample types, one location Multiple sample types, multiple locations Insufficient information to determine	Higher risk of bias Reviewer judgement required - Lower risk of bias OR higher risk of bias Lower risk of bias Lower risk of bias Higher risk of bias
Outcome measurement	How was mortality measured?	Death registry or death certificate data Medical record, personal contacts, or other source Insufficient information to determine	Lower risk of bias Higher risk of bias Higher risk of bias
QUALITY OF REPORTING DOMAINS			
	Description	**Options**	**Rating**
Completeness of cohort characterisation	Was the cohort adequately described in terms of age (mean/median, or categorical age data) and sex?	No – study did not report age or sex data for sample Yes – Age and sex data for the sample was reported	Lower quality of reporting Higher quality of reporting
Completeness of outcome data	Did the study report both numerator and denominator for main outcome analysis?	No – Numerator, denominator, or both missing Yes – numerator and denominator reported for main outcome analysis	Lower quality of reporting Higher quality of reporting
Definitions use for cause-specific deaths reported	Did the study report the definitions used for cause-specific deaths i.e. ICD codes	N/A – the study did not report cause-specific deaths No – no definitions provided (e.g. the study states only “we calculated overdose mortality rates” without explaining how overdose was defined)	N/A Lower quality of reporting

		Yes – The study provides ICD codes or other information to describe the definition of cause-specific deaths	Higher quality of reporting

Note. [a] Examples of coding for sample representativeness used for guidance comprised:

1. A cohort recruited from a single hospital = one sample type, one location
2. A cohort recruited through drug treatment and harm reduction services in a single city or neighbourhood = multiple sample types, one location
3. A cohort recruited through respondent-driven/street-based/convenience sampling = multiple sample types, multiple locations
4. A cohort identified from a database that includes data on people presenting to treatment from a large geographical area = one sample type, multiple locations
5. A cohort identified from a database that includes data on people presenting to treatment from a restricted geographical area = one sample type, one location
6. A cohort identified from different databases (e.g., drug treatment database, criminal justice database) from a large geographic area = multiple sample types, multiple locations

Exceptions:

7. A cohort comprising a very high-risk population for mortality (e.g., people who are incarcerated) = always single sample type and high risk, regardless of number of locations
8. A cohort with insufficient information about sample types/site locations = higher risk of bias

Appendix H: Data derived and calculation methods

Crude Mortality Rate (CMR)

If the study failed to report all relevant information related to CMR, the following equations were used to calculate the missing information. Confidence interval and standard error calculations were completed on the log scale to bound the results between 0 and +∞ and to account for deaths being a rarer event.

$$\text{CMR (per 100 PY)} = 100 \text{ x } \frac{\text{Observed deaths}}{\text{PYFU}}$$

CMR 95% confidence interval:

$$\ln(\text{CMR lci}) = \ln(\text{CMR}) - 1.96\left(\frac{1}{\sqrt{\text{observed deaths}}}\right)$$

$$\ln(\text{CMR uci}) = \ln(\text{CMR}) + 1.96\left(\frac{1}{\sqrt{\text{observed deaths}}}\right)$$

CMR standard error:

$$\text{SE (lnCMR)} = \frac{1}{\sqrt{\text{observed deaths}}}$$

Where: PY = person years; PYFU = person years of follow-up; lci = lower confidence interval; uci = upper confidence interval; SE = standard error.

Studies that reported deaths and follow up, but not person years

For studies that did not report person years, PYFU were estimated.

The hierarchy of information used to calculate PYFU was 1) drug-specific median FU, 2) drug-specific mean FU, 3) cohort median FU, 4) cohort mean FU, 5) reported FU period then 6) study length.

Due to the proportion of mortality within the cohorts, median was preferred over mean to minimise the potential that the calculated PYFU would be more reflective of the proportion of the cohort who were alive at the conclusion of FU/the study, than the proportion who died. As there were studies who following people who use more than one type of drug, drug-specific data was preferred to better reflective our population of interest; people with regular or problematic use of cocaine. Reported FU period and study length were lower on the hierarchy as there is more potential of bias due to an assumption of when deaths occurred being needed. Reported FU period was given higher preference as the data would be more informative than study length. Where median or mean follow-up period was reported, person year follow up was calculated using:

$$\text{PYFU} = \text{N x (median or mean FU)}$$

For example, if a study reported that people who used cocaine (N = 100) were followed for a median of 2.5 years, PYFU would be calculated as:

$$\text{PYFU} = 100 \text{ x } 2.5 \text{ years} = 250 \text{ PYFU}$$

For studies where there was no median or mean follow-up period, the study reported follow-up period or study length was used to calculate PYFU using (assuming all deaths occurred halfway through follow-up):

$$\text{PYFU} = (\text{n}_{alive} \text{ x study period}) + (\text{n}_{dead} \text{ x } \frac{\text{study period}}{2})$$

For example, if a study of 200 people who used cocaine reported that there were 23 deaths within the 6 years of follow-up, PYFU would be calculated as:

$$\text{PYFU} = ((200\text{-}23) \text{ x } 6) + (23 \text{ x } (6/2)) = (177 \text{ x } 6) + (23 \text{ x } 3) = 1131 \text{ PYFU}$$

This was our a priori hierarchy for selection of information. However, when we extracted the data, we found no studies that reported median or mean, and thus we were required to use reported FU period and study length.

Standardised Mortality Ratio (SMR)

If the study failed to report all relevant information related to SMR, the following equations were used to calculate the missing information.

$$\text{SMR} = \frac{\text{Observed deaths}}{\text{Expected deaths}}$$

To calculate missing confidence intervals, OpenEpi SMR calculator was used (www.openepi.com/S MR/SMR.htm). OpenEpi is an online, open-source tool created for epidemiologic calculations. The confidence intervals calculated via the Mid-P exact test was used to fill in the missing information. More information can be located on their website about the test (http://www.openepi.com).

SMR standard error:

$$\text{SMR SE} = \frac{(\text{SMR uci} - \text{SMR lci})}{3.92}$$

Imputing SMRs using data from the Global Burden of Disease study

When CMR was able to be calculated but no relevant SMR data was reported, a SMR was estimated using Global Burden of Disease 2017 (GBD) data. To be able to estimate SMR, all deaths were assumed to occur at the midpoint of the study period. GBD data was accessed through http://ghdx.healthdata.org/gbd-results-tool and matched as closely as possible to the location of study, age range of participants at midpoint and midpoint year of the study. As cocaine use was limited to problematic or harmful use, a prevalence rate for cocaine dependence was calculated using the GBD data as well as a mortality rate for the associated general population. A SMR and relative risk (RR) were then estimated by comparing to study CMR to GBD calculated mortality and prevalence rate.

Relative Risk (RR)

Prior to calculating the RR, the prevalence of cocaine dependence in the population was calculated using Global Burden of Disease 2017 (GBD) data. As with the inputting of SMRs, the data was as closely matched to location of study, age range of participants and year at study midpoint. Estimating RRs from SMRs was based on the methodology outlined by Jones and Swerdlow [8].

$$\text{Prevalence in population} = \frac{\text{Total number of users}}{\text{Total population}}$$

To calculate RR and its confidence interval, the following equation was used:

$$\text{Relative Risk} = \frac{\text{SMR x } (1 - \text{Prevalence in population})}{1 - (\text{Prevalence in population x SMR})}$$

Table H1: Contrasting estimated CMRs with those reported in studies with author-reported CMRs

Study	Follow-up (years)	Cohort N	Deaths	PYFU	Reported CMR (95% CI) (/100 PY)	Calculated PYFU	Calculated CMR (95% CI) (/100PY)
Barrio et al., 2013[9]	Mean for cocaine: 5.07	714	9	3922	0.23 (0.12, 0.44)	3619.98 (714 * 5.07)	0.25 (0.13, 0.48)
Callaghan et al., 2013[10]	01/01/1990 – 31/12/2005 (16)	48949	4356	395738	1.10 (1.07, 1.13)	748336 [((48949 – 4356)*16)+(4356*8)]	0.58 (0.57, 0.60)
Hayashi et al., 2016[11]	Median for all: 5.05	1719	392	11748.63	3.34 (3.02, 3.68)	8680.95 (1719 * 5.05)	4.52 (4.09, 4.99)
Lopez et al., 2004[12]	1992-2001 (9)	2212	80	11496	0.70 (0.56, 0.87)	19548 [((2212-80)*9) + (80 *4.5)]	0.41 (0.33, 0.51)
Sanvisens et al., 2014[13]	Median for cocaine: 6.5	945	202	7155	2.8 (2.5, 3.2)	6142.5 (945 * 6.5)	3.29 (2.87, 3.78)
van Haastrecht et al., 1996{van Haastrecht, 1996 #217}	01/12/1985 - 01/02/1993 (7.17)	Not reported	9	194	4.64 (2.41, 8.92)	-	-
Vlahov et al., 2008{Vlahov, 2008 #208}	1997 - 31/12/2002 (6)	102	3	485.7	0.62 (0.20, 1.92)	603 [((102-3)*6)+(3*3)]	0.50 (0.16, 1.54)
Wang et al., 2005{Wang, 2005 #218}	1988 – 31/12/2001 (14)	518	175	3727	4.69 (4.03, 5.45)	6027 [((518-175)*14)+(175*7)]	2.90 (2.50, 3.36)

Appendix I: Excluded studies

Small cohort (n< 30)

1. Dibu J, Yaghi S, Achi E, Patel A, Samant R, Hinduja A. Intracerebral hemorrhage associated with cocaine use. Neurology Conference: 65th American Academy of Neurology Annual Meeting San Diego, CA United States Conference Publication:. 2013;80(1 MeetingAbstracts).
2. Galvin S, Campbell M, Marsh B, O'Brien B. Cocaine-related admissions to an intensive care unit: A five-year study of incidence and outcomes. Anaesthesia. 2010;65(2):163-6. doi:10.1111/j.1365-2044.2009.06189.x
3. Manini AF, Hoffman RS, Vlahov D. Agitated delirium and risk of adverse cardiovascular events following acute overdose. Clinical Toxicology. 2012;50 (4)(4):317.

Case report/case-series

1. Ahmed I, Bart G, Bart BA. Cocaine users hospitalized for acute decompensated heart failure: Falling between the cracks e an opportunity for improved care. Journal of Cardiac Failure. 2010;1):S109.
2. Akpunonu P, Hendrickson R, Gerona R. A pinhead dose brings the death bed close. Clinical Toxicology. 2017;55 (7)(7):757.
3. Al-Abri S, Huntington S, Geller R, Olson K, Carlson T. Poisonings among California inmates 2011-2013. Clinical Toxicology. 2014;52 (7)(7):749-50.
4. Alaraj A, Wallace A, Mander N, Aletich V, Charbel FT, Amin-Hanjani S. Effect of acute cocaine use on vasospasm and outcome in aneurysmal subarachnoid hemorrhage. World Neurosurgery. 2010;73(4):357-60. doi:10.1016/j.wneu.2010.01.011
5. Alison D, Dargan PI, Heyerdahl F, Hvoda KE, Yates C, Giraudon I, et al. Four months surveillance of recreational drug use in Europe: First report from the European Drug Emergencies Network (Euro-DEN) project. Clinical Toxicology. 2014;52 (7)(7):703.
6. Armenian P, Dirks R, Kaups KL. Cocaine and alcohol result in worse outcomes in Trauma patients than amphetamines and alcohol. Clinical Toxicology. 2015;53 (7)(7):673-4.
7. Atoui M, Fida N, Nayudu SK, Glandt M, Chilimuri S. Outcomes of patients with cocaine induced chest pain in an inner city hospital. Cardiology Research. 2011;2(6):269-73. doi:10.4021/cr103w
8. Bahorik AL, Satre DD, Kline-Simon AH, Weisner CM, Campbell CI. Alcohol, Cannabis, and Opioid Use Disorders, and Disease Burden in an Integrated Health Care System. Journal of Addiction Medicine. 2017;11(1):3-9. doi:10.1097/Adm.0000000000000260
9. Bajwa AA, Silliman S, Cury JD, Seeram V, Shujaat A, Usman F, et al. Characteristics and outcomes of cocaine-related spontaneous intracerebral hemorrhages. ISRN Neurology. 2013;1 (1) (no pagination)(124390):124390. doi:10.1155/2013/124390
10. Beasley GM, Ostbye T, Muhlbaier LH, Foley C, Scarborough J, Turley RS, et al. Age and gender differences in substance screening may underestimate injury severity: A study of 9793 patients at level 1 trauma center from 2006 to 2010. Journal of Surgical Research. 2014;188(1):190-7. doi:10.1016/j.jss.2013.11.1103
11. Bohnert AS, Prescott MR, Vlahov D, Tardiff KJ, Galea S. Ambient temperature and risk of death from accidental drug overdose in New York City, 1990-2006. Addiction (Abingdon, England). 2010;105(6):1049-54. doi:10.1111/j.1360-0443.2009.02887.x
12. Borriello R, Carfora A, Cassandro P, Petrella R. A five years study on drug-related deaths in Campania (Italy). Annali dell'Istituto superiore di sanita. 2014;50(4):328-33. doi:10.4415/ANN_14_04_06
13. Buxton JA, Skutezky T, Tu AW, Waheed B, Wallace A, Mak S. The context of illicit drug overdose deaths in British Columbia, 2006. Harm Reduction Journal. 2009;6 (no pagination)(9):9. doi:10.1186/1477-7517-6-9
14. Calcaterra S, Binswanger IA. Comparative overdose death rates between illicit and prescribed substances. Journal of General Internal Medicine. 2012;2):S145.

15. Calcaterra S, Binswanger IA. National trends in psychostimulant-related deaths: 1999-2009. Substance abuse : official publication of the Association for Medical Education and Research in Substance Abuse. 2013;34(2):129-36. doi:10.1080/08897077.2012.726959
16. Calcaterra S, Blatchford P, Friedmann PD, Binswanger IA. Psychostimulant-related deaths among former inmates. Journal of Addiction Medicine. 2012;6(2):97-105. doi:10.1097/ADM.0b013e318239c30a
17. Cerda M, Messner SF, Tracy M, Vlahov D, Goldmann E, Tardiff KJ, et al. Investigating the effect of social changes on age-specific gun-related homicide rates in New York City during the 1990s. American Journal of Public Health. 2010;100(6):1107-15. doi:10.2105/AJPH.2008.158238
18. Cerda M, Ransome Y, Keyes KM, Koenen KC, Tracy M, Tardiff KJ, et al. Prescription opioid mortality trends in New York City, 1990-2006: Examining the emergence of an epidemic. Drug and Alcohol Dependence. 2013;132(1-2):53-62. doi:10.1016/j.drugalcdep.2012.12.027
19. Chachamovich E, Ding Y, Turecki G. Levels of aggressiveness are higher among alcohol-related suicides: Results from a psychological autopsy study. Alcohol. 2012;46(6):529-36. doi:10.1016/j.alcohol.2012.03.007
20. Chang TR, Kowalski RG, Caserta F, Carhuapoma JR, Tamargo RJ, Naval NS. Impact of acute cocaine use on aneurysmal subarachnoid hemorrhage. Stroke. 2013;44(7):1825-9. doi:10.1161/STROKEAHA.111.000749
21. Cheng V, Inaba K, Johnson M, Byerly S, Jiang Y, Matsushima K, et al. The impact of pre-injury controlled substance use on clinical outcomes after trauma. The Journal of Trauma and Acute Care Surgery. 2016;81(5):913-20. doi:10.1097/TA.0000000000001229
22. Cheng WC, Dao KL. The occurrence of alcohol/drugs by toxicological examination of selected drivers in Hong Kong. Forensic Science International. 2017;275:242-53. doi:10.1016/j.forsciint.2017.03.022
23. Elramah M, Einstein M, Mori N, Vakil N. High mortality of cocaine-related ischemic colitis: A hybrid cohort/case-control study. Gastrointestinal Endoscopy. 2012;75(6):1226-32. doi:10.1016/j.gie.2012.02.016
24. Eskandar A, Mahdi F, Punnakkattu R. Respiratory failure secondary to drug overdose causes and demographics. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2014;189(MeetingAbstracts).
25. Fareed A, Casarella J, Amar R, Vayalapalli S, Drexler K. Benefits of retention in methadone maintenance and chronic medical conditions as risk factors for premature death among older heroin addicts. Journal of Psychiatric Practice. 2009;15(3):227-34. doi:DOI 10.1097/01.pra.0000351884.83377.e2
26. Galicia M, Nogue S, Miro O. Liquid ecstasy intoxication: clinical features of 505 consecutive emergency department patients. Emergency Medicine Journal. 2011;28(6):462-6. doi:10.1136/emj.2008.068403
27. Garg M, Kettel kamp RT. Continued cocaine use and re admission in patients with cocaine-related acute coronary syndrome. Journal of Investigative Medicine. 2012;60 (4)(4):725.
28. Guollo F, Narciso-Schiavon JL, Barotto AM, Zannin M, Schiavon LL. Significance of alanine aminotransferase levels in patients admitted for cocaine intoxication. Journal of Clinical Gastroenterology. 2015;49(3):250-5. doi:10.1097/MCG.0000000000000056
29. Gupta N, Washam JB, Mountantonakis SE, Li S, Roe MT, de Lemos JA, et al. Characteristics, management, and outcomes of cocaine-positive patients with acute coronary syndrome (from the National Cardiovascular Data Registry). American Journal of Cardiology. 2014;113(5):749-56. doi:10.1016/j.amjcard.2013.11.023
30. Hadjizacharia P, Green DJ, Plurad D, Chan LS, Law J, Inaba K, et al. Cocaine use in trauma: Effect on injuries and outcomes. Journal of Trauma - Injury, Infection and Critical Care. 2009;66(2):491-4. doi:10.1097/TA.0b013e3181622b9b

31. Heninger M. Subdural hematoma occurrence: comparison between ethanol and cocaine use at death. The American journal of forensic medicine and pathology. 2013;34(3):237-41. doi:10.1097/PAF.0b013e3182834b32
32. Jayarajan S, Taghavi S, Komaroff E, Shiose A, Schwartz D, Hamad E, et al. Long-term outcomes in heart transplantation using donors with a history of past and present cocaine use. European Journal of Cardio-thoracic Surgery. 2015;47(4):e146-e50. doi:10.1093/ejcts/ezu512
33. Jones AW, Holmgren A. Concentrations of cocaine and benzoylecgonine in femoral blood from cocaine-related deaths compared with venous blood from impaired drivers. Journal of Analytical Toxicology. 2014;38(1):46-51. doi:10.1093/jat/bkt094
34. Jones CM, Baldwin GT, Compton WM. Recent increases in cocaine-related overdose deaths and the role of opioids. American Journal of Public Health. 2017;107(3):430-2. doi:10.2105/Ajph.2016.303627
35. Laberke PJ, Bartsch C. Trends in methadone-related deaths in Zurich. International journal of legal medicine. 2010;124(5):381-5. doi:10.1007/s00414-010-0442-8
36. Mack K. Overdoses of opioids and other drugs among women United States, 1999-2014. Journal of Women's Health. 2017;26 (4)(4):A37.
37. Maloney GE, Bryant SM. Cocaine abuse in older adults; baby boomers & blow in the nursing home. Clinical Toxicology. 2011;49 (6)(6):527.
38. Marinov P, Zlateva S, Bonchev G, Ivanov D, Georgiev K, Sabeva Y, et al. Acute narcotic drug intoxications: Etiology, sex/age distribution and clinical outcome. Journal of IMAB - Annual Proceeding (Scientific Papers). 2017;23(1):1444-6. doi:10.5272/jimab.2017231.1444
39. Martin-Schild S, Albright KC, Misra V, Philip M, Barreto AD, Hallevi H, et al. Intravenous tissue plasminogen activator in patients with cocaine-associated acute ischemic stroke. Stroke. 2009;40(11):3635-7. doi:10.1161/STROKEAHA.109.559823
40. McLaughlin AM, Hardt J, McKay AP, Fitzpatrick GJ, Donnelly MB. Alcohol, drug misuse and suicide attempts: Unrecognised causes of out of hospital cardiac arrests admitted to intensive care units. Irish Journal of Medical Science. 2009;178(1):29-33. doi:10.1007/s11845-008-0242-z
41. Murthy SB, Moradiya Y, Shah S, Naval NS. In-hospital outcomes of aneurysmal subarachnoid hemorrhage associated with cocaine use in the USA. Journal of Clinical Neuroscience. 2014;21(12):2088-91. doi:10.1016/j.jocn.2014.05.012
42. Newsome SD, Johnson E, Pardo C, McArthur JC, Nath A. Fulminant encephalopathy with basal ganglia hyperintensities in HIV-infected drug users. Neurology. 2011;76(9):787-94. doi:10.1212/WNL.0b013e31820e7b4e
43. O'Brien BP, Murphy D, Conrick-Martin I, Marsh B. The functional outcome and recovery of patients admitted to an intensive care unit following drug overdose: a follow-up study. Anaesthesia & Intensive Care. 2009;37(5):802-6.
44. Samuel V, Singh A, Cury J, Shujaat A, Bajwa A. Prevalence of cocaine use in patients with intraparenchymal hemorrhage (IPH). Chest Conference: CHEST. 2011;140(4 MEETING ABSTRACT).
45. Singh V, Rodriguez AP, Thakkar B, Savani GT, Patel NJ, Badheka AO, et al. Hospital Admissions for Chest Pain Associated with Cocaine Use in the United States. American Journal of Medicine. 2017;130(6):688-98. doi:10.1016/j.amjmed.2016.12.003
46. Sofidiotou V, Dolianiti M, Basanou E, Kalostou A, Fountas K, Touloupaki V, et al. Drugs of abuse used by patients presenting to the Emergency Department over a one year period. Clinical Toxicology. 2016;54 (4)(4):400.
47. Sue K, Hubbeling H, Kuo C, Brubaker K, Xu L, Fernandez-Golarz C, et al. Post-prison blues: Utilizing a primary care student-faculty collaborative clinic to concurrently treat heroin addiction, ptsd and hepatitis C. Journal of General Internal Medicine. 2014;1):S411.
48. Truszkowska E, McCarron P, Konovalov P, Galander T, Lyons S, Keenan E, et al. Case-control study of risks and causes of death amongst opioid dependent patients on methadone maintenance treatment. Canadian Journal of Addiction. 2015;6(3):18-26.

49. Wiener SE, Sutijono D, Moon CH, Subramanian RA, Calaycay J, Rushbrook JI, et al. Patients with detectable cocaethylene are more likely to require intensive care unit admission after trauma. American Journal of Emergency Medicine. 2010;28(9):1051-5. doi:10.1016/j.ajem.2009.06.014
50. Yeung JT, Williams J, Bowling WM. Effect of cocaine use on outcomes in traumatic brain injury. Journal of Emergencies, Trauma and Shock. 2013;6(3):189-94.
51. Zilker T. Occurrence of poisoning over 50 years treated in the Munich center. Clinical Toxicology. 2012;50 (4)(4):295.

Editorial or review

1. Amundsen EJ. Aspects of high-risk drug use estimation: The Norwegian experience. Nordic Studies on Alcohol and Drugs. 2013;30(3):167-8. doi:10.2478/nsad-2013-0012
2. Amundsen EJ, Bretteville-Jensen AL. Hard drug use in Norway. NAT Nordisk alkohol & narkotikatidskrift. 2010;27(1):87-94.
3. An SJ, Kim TJ, Yoon BW. Epidemiology, risk factors, and clinical features of intracerebral hemorrhage: An update. Journal of Stroke. 2017;19(1):3-10. doi:10.5853/jos.2016.00864
4. Calle S, Thys C, Tanushi G, De Groote L, Calle P. Cerebrovascular complications of substance abuse. [Dutch]. Tijdschrift voor Geneeskunde. 2017;73(22):1379-85.
5. Centers for Disease C, Prevention. Drug overdose deaths--Florida, 2003-2009. MMWR - Morbidity & Mortality Weekly Report. 2011;60(26):869-72.
6. Centers for Disease C, Prevention. Buprenorphine prescribing practices and exposures reported to a poison center--Utah, 2002-2011. MMWR - Morbidity & Mortality Weekly Report. 2012;61(49):997-1001.
7. Eiden C, Diot C, Mathieu O, Mallaret M, Peyriere H. Levamisole-adulterated cocaine: what about in European countries? Journal of Psychoactive Drugs. 2014;46(5):389-92. doi:10.1080/02791072.2014.959215
8. McDonald RD, Tofighi B, Laska E, Goldfeld K, Bonilla W, Flannery M, et al. Extended-release naltrexone opioid treatment at jail reentry (XOR). Contemporary Clinical Trials. 2016;49:57-64. doi:10.1016/j.cct.2016.05.002
9. Mounteney J, Griffiths P, Sedefov R, Noor A, Vicente J, Simon R. The drug situation in Europe: an overview of data available on illicit drugs and new psychoactive substances from European monitoring in 2015. Addiction (Abingdon, England). 2016;111(1):34-48. doi:10.1111/add.13056
10. Riley ED, Cohen J, Shumway M. Overdose fatality and surveillance as a method for understanding mortality trends in homeless populations. JAMA Internal Medicine. 2013;173(13):1264. doi:10.1001/jamainternmed.2013.6838
11. Saper JR, Lake IAE, Bain PA, Stillman MJ, Rothrock JF, Mathew NT, et al. A practice guide for continuous opioid therapy for refractory daily headache: Patient selection, physician requirements, and treatment monitoring. Headache. 2010;50(7):1175-93. doi:10.1111/j.1526-4610.2010.01733.x

No mortality data among people who use drug

1. Akpa B, Nwazue V, Bhoggireddy V, Okafor H. A three year retrospective analysis of adverse cardiac outcomes in heart failure patients using cocaine on beta-blockers. Circulation Conference: American Heart Association's. 2014;130(SUPPL. 2).
2. Arendt M, Munk-Jorgensen P, Sher L, Jensen SOW. Mortality following treatment for cannabis use disorders: Predictors and causes. Journal of Substance Abuse Treatment. 2013;44(4):400-6. doi:10.1016/j.jsat.2012.09.007
3. Atkinson TS, Sanders N, Mancino M, Oliveto A. Effects of disulfiram on QTc interval in non-opioid-dependent and methadone-treated cocaine-dependent patients. Journal of Addiction Medicine. 2013;7(4):243-8. doi:10.1097/ADM.0b013e3182928e02

4. Esteban MR, Montero SM, Sanchez JJA, Hernandez HP, Perez JJG, Afonso JH, et al. Acute coronary syndrome in the young: Clinical characteristics, risk factors and prognosis. Open Cardiovascular Medicine Journal. 2014;8(1):61-7. doi:10.2174/1874192401408010061
5. Jones A, Hayhurst KP, Millar T, Pierce M, Dunn G, Donmall M. Short-Term Outcomes for Opiate and Crack Users Accessing Treatment: The Effects of Criminal Justice Referral and Crack Use. European Addiction Research. 2016;22(3):145-52. doi:10.1159/000438987
6. Salihu HM, Salemi JL, Aggarwal A, Steele BF, Pepper RC, Mogos MF, et al. Opioid Drug Use and Acute Cardiac Events Among Pregnant Women in the United States. American Journal of Medicine. 2018;131(1):64-71.e1. doi:10.1016/j.amjmed.2017.07.023
7. Wong SS, Zhou B, Goebert D, Hishinuma ES. The risk of adolescent suicide across patterns of drug use: a nationally representative study of high school students in the United States from 1999 to 2009. Social psychiatry and psychiatric epidemiology. 2013;48(10):1611-20. doi:10.1007/s00127-013-0721-z

Unclear intentional use of drug

1. Armenian P, Fleurat M, Mittendorf G, Olson KR. Unintentional Pediatric Cocaine Exposures Result in Worse Outcomes than Other Unintentional Pediatric Poisonings. Journal of Emergency Medicine. 2017;52(6):825-32. doi:10.1016/j.jemermed.2017.03.017

Mortality data but required variables not reported

1. Kendler KS, Ohlsson H, Sundquist K, Sundquist J. Drug abuse-associated mortality across the lifespan: A population-based longitudinal cohort and co-relative analysis. Social psychiatry and psychiatric epidemiology. 2017;52(7):877-86. doi:10.1007/s00127-017-1398-5
2. Lovrecic B, Semerl JS, Tavcar R, Maremmani I. Sociodemographic and clinical differences among deceased and surviving cohort members of opioid maintenance therapy. Heroin Addiction and Related Clinical Problems. 2011;13(3):39-48.
3. Qureshi A, Suri M. Cocaine use and the likelihood of cardiovascular and all-cause mortality: Data from the third national health and nutrition examination survey mortality follow-up study. Neurology Conference: 64th American Academy of Neurology Annual Meeting New Orleans, LA United States Conference Publication:. 2012;78(1 Meeting Abstract).
4. Rangel C, Shu RG, Lazar LD, Vittinghoff E, Hsue PY, Marcus GM. Beta-blockers for chest pain associated with recent cocaine use. Archives of Internal Medicine. 2010;170(10):874-9. doi:DOI 10.1001/archinternmed.2010.115
5. Schenberg EE, de Castro Comis MA, Chaves BR, da Silveira DX. Treating drug dependence with the aid of ibogaine: a retrospective study. Journal of Psychopharmacology. 2014;28(11):993-1000. doi:10.1177/0269881114552713
6. Walker ER, Pratt LA, Schoenborn CA, Druss BG. Excess mortality among people who report lifetime use of illegal drugs in the United States: A 20-year follow-up of a nationally representative survey. Drug and Alcohol Dependence. 2017;171:31-8. doi:10.1016/j.drugalcdep.2016.11.026

Not a cocaine using cohort (<90%)

1. Abdelfattah A, Allam AH, Aaty AA, Albaghdadi M, Huffman M, Kholeif H, et al. Differences in clinical presentation, management, and outcomes in acute coronary syndrome by age group: Results from the egyptian center of excellence registry for acute coronary syndromes. Circulation. 2012;125 (19)(19):e802-e3.

2. Aguilera P, Garrido M, Lessard E, Swanson J, Mallon WK, Saldias F, et al. Medication overdoses at a public emergency department in santiago, Chile. Western Journal of Emergency Medicine. 2016;17(1):75-80. doi:10.5811/westjem.2015.11.26068
3. Allison RD, Conry-Cantilena C, Koziol D, Schechterly C, Ness P, Gibble J, et al. A 25-year study of the clinical and histologic outcomes of hepatitis C virus infection and its modes of transmission in a cohort of initially asymptomatic blood donors. Journal of Infectious Diseases. 2012;206(5):654-61. doi:10.1093/infdis/jis410
4. Amro O, Ibrahim A, Mayasy S, Ravakhah K, Sopko J, Merugu S, et al. Predictors of major cardiac adverse events in patients with carbon monoxide poisoning. Journal of General Internal Medicine. 2012;2):S276.
5. Andrade-Villanueva J, Gonzalez-Hernandez L, Llamas-Covarrubias M, Ponce-Herrera D, Soria-Rodriguez R, Zuniga-Quinonez S, et al. Evaluation of HIV-infection control, risk behaviours and comorbidities among inmates in Mexico. Journal of the International AIDS Society. 2015;2):14.
6. Andreuccetti G, Leyton V, Miziara ID, Lemos NP, Munoz DR, Cherpitel CJ, et al. Introducing a new research method for evaluating alcohol and other drug use among fatally injured victims in Latin America. Drug and Alcohol Dependence. 2017;171:e8-e9.
7. Andrew E,Tellerup M, Terml AM, Jacobsen P, Gudjonsdottir GA. Poisonings in the Nordic countries in 2007: A 5-year epidemiological follow-up. Clinical Toxicology. 2012;50(3):210-4.
8. Bartolucci J, Nazzal NC, Verdugo FJ, Prieto JC, Sepulveda P, Corbalan R. Characteristics, management, and outcomes of illicit drug consumers with acute myocardial infarction. [Spanish]. Revista Medica de Chile. 2016;144(1):39-46.
9. Bjornaas MA, Teige B, Hovda KE, Ekeberg O, Heyerdahl F, Jacobsen D. Fatal poisonings in Oslo: A one-year observational study. BMC Emergency Medicine. 2009;10 (no pagination)(13).
10. Blount RJ, Stone SA, Falahati V, Auld E, Balmes JR, Huang L. Common inhaled toxins associated with pulmonary infection in HIV-infected patients admitted to an urban hospital. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2014;189(MeetingAbstracts).
11. Bohnert ASB, Ilgen MA, Galea S, McCarthy JF, Blow FC. Accidental poisoning mortality among patients in the Department of Veterans Affairs health system. Medical Care. 2011;49(4):393-6. doi:10.1097/MLR.0b013e318202aa27
12. Bougouin W, Karam N, Sharifzadehgan A, Narayanan K, Varenne O, Spaulding C, et al. Sudden cardiac arrest related to coronary vasospasm: Frequency, characteristics and outcomes. Circulation Conference: Resuscitation Science Symposium, ReSS. 2017;136(Supplement 1).
13. Caira M, Candoni A, Verga L, Busca A, Delia M, Nosari A, et al. Pre-chemotherapy risk factors for invasive fungal diseases: prospective analysis of 1,192 patients with newly diagnosed acute myeloid leukemia (SEIFEM 2010-a multicenter study). Haematologica. 2015;100(2):284-92. doi:10.3324/haematol.2014.113399
14. Carrellas NW, Fitzgerald M, Rosenthal L, McKowen J, Nargiso J, Bergman B, et al. Risk factors associated with overdose during follow-up in treatment-seeking youth with substance use disorders. Journal of the American Academy of Child and Adolescent Psychiatry. 2017;56 (10):S295-S6.
15. Carrillo X, Curos A, Muga R, Serra J, Sanvisens A, Bayes-Genis A. Acute coronary syndrome and cocaine use: 8-year prevalence and inhospital outcomes. European Heart Journal. 2011;32(10):1244-50. doi:10.1093/eurheartj/ehq504
16. Chang G, Meadows ME, Jones JA, Antin JH, Orav EJ. Substance use and survival after treatment for chronic myelogenous leukemia (CML) or myelodysplastic syndrome (MDS). American Journal of Drug & Alcohol Abuse. 2010;36(1):1-6. doi:10.3109/00952990903490758
17. Chang TR, Kowalski RG, Carhuapoma JR, Tamargo RJ, Naval NS. Impact of case volume on aneurysmal subarachnoid hemorrhage outcomes. Journal of Critical Care. 2015;30(3):469-72. doi:10.1016/j.jcrc.2015.01.007

18. Cogswell R, Smith E, Hamel A, Bauman L, Herr A, Duval S, et al. Substance abuse at the time of left ventricular assist device implantation is associated with increased mortality. Journal of Heart and Lung Transplantation. 2014;33(10):1048-55. doi:10.1016/j.healun.2014.06.009
19. Cohn SE, Jiang H, McCutchan JA, Koletar SL, Murphy RL, Robertson KR, et al. Association of ongoing drug and alcohol use with non-adherence to antiretroviral therapy and higher risk of AIDS and death: Results from ACTG 362. AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV. 2011;23(6):775-85. doi:10.1080/09540121.2010.525617
20. Cooper LB, Lu D, Mentz RJ, Rogers JG, Milano CA, Felker GM, et al. Cardiac transplantation for older patients: Characteristics and outcomes in the septuagenarian population. Journal of Cardiac Failure. 2015;1)(3):S9. doi:10.1016/j.healun.2015.10.028
21. Copeland L, Robertson J, McKenzie J, Kimber J, Macleod J, Hickman M, et al. Premature mortality in scottish injecting drug users: A life-history approach. Scottish Medical Journal. 2012;57(1):38-42. doi:10.1258/smj.2011.011289
22. Dangayach NS, Zammit C, Bruce R, Connolly S, Schmidt M, Claassen J, et al. Predicting acute mortality in patients with ICH: Beyond the ICH score. Neurocritical Care. 2013;1):S32.
23. Demarie D, Marletta G, Imazio M, Cappa C, Ferro S, Compostino R, et al. Cardiovascular-associated disease in an addicted population: an observation study. Journal of Cardiovascular Medicine. 2011;12(1):51-4. doi:10.2459/JCM.0b013e32834033f2
24. Dines AM, Wood DM, Yates C, Heyerdahl F, Hovda KE, Giraudon I, et al. Acute recreational drug and new psychoactive substance toxicity in Europe: 12 months data collection from the European Drug Emergencies Network (Euro-DEN). Clinical Toxicology: The Official Journal of the American Academy of Clinical Toxicology & European Association of Poisons Centres & Clinical Toxicologists. 2015;53(9):893-900. doi:10.3109/15563650.2015.1088157
25. Escaned J, Echavarria-Pinto M, Gorgadze T, Gonzalo N, Armengol F, Hernandez R, et al. Safety of lone thrombus aspiration without concomitant coronary stenting in selected patients with acute myocardial infarction. EuroIntervention. 2013;8(10):1149-56. doi:10.4244/Eijv8i10a178
26. Evans E, Kelleghan A, Li L, Min J, Huang D, Urada D, et al. Gender differences in mortality among treated opioid dependent patients. Drug and Alcohol Dependence. 2015;155:228-35. doi:10.1016/j.drugalcdep.2015.07.010
27. Evans JL, Tsui JI, Hahn JA, Davidson PJ, Lum PJ, Page K. Mortality among young injection drug users in San Francisco: A 10-year follow-up of the UFO study. American Journal of Epidemiology. 2012;175(4):302-8. doi:10.1093/aje/kwr318
28. Fareed A, Vayalapalli S, Byrd-Sellers J, Casarella J, Drexler K. Safety and efficacy of long-term buprenorphine maintenance treatment. Addictive Disorders and their Treatment. 2011;10(3):123-30. doi:10.1097/ADT.0b013e318211ba0a
29. Fareed A, Vayalapalli S, Scheinberg K, Gale R, Casarella J, Drexler K. QTc interval prolongation for patients in methadone maintenance treatment: A five years follow-up study. American Journal of Drug and Alcohol Abuse. 2013;39(4):235-40. doi:10.3109/00952990.2013.804525
30. Galicia M, Nogue S, Burillo-Putze G. Ten years of emergency attendances for cocaine-users in Spain. [Spanish]. Medicina Clinica. 2014;143(7):322-6.
31. Garg J, Krishnamoorthy P, Palaniswamy C, Pandey A, Ahmad H. Predictors of in-hospital mortality in coronary artery dissection: Findings from the National Inpatient Sample 2009-2010. Cardiology Journal. 2015;22(2):135-40. doi:10.5603/CJ.a2014.0048
32. Goldman-Hasbun J, DeBeck K, Buxton JA, Nosova E, Wood E, Kerr T. Knowledge and possession of take-home naloxone kits among street-involved youth in a Canadian setting: A cohort study. Harm Reduction Journal. 2017;14 (1) (no pagination)(79). doi:ARTN 79 10.1186/s12954-017-0206-6
33. Herdener M, Dursteler KM, Seifritz E, Nordt C. Changes in substance use in patients receiving opioid substitution therapy and resulting clinical challenges: a 17-year treatment case register analysis. The Lancet Psychiatry. 2017;4(4):302-9. doi:10.1016/S2215-0366(17)30080-9

34. Hickman M, Hope V, Coleman B, Parry J, Telfer M, Twigger J, et al. Assessing IDU prevalence and health consequences (HCV, overdose and drug-related mortality) in a primary care trust: implications for public health action. Journal of public health (Oxford, England). 2009;31(3):374-82. doi:10.1093/pubmed/fdp067
35. Hjorthoj CR, Ostergaard M, Benros ME, Toftdahl NG, Erlangsen A, Andersen JT, et al. The contribution of substance use disorders to mortality in schizophrenia. Schizophrenia Bulletin. 2015;1):S142.
36. Hlavacek CM. The effect of illicit drugs on mortality and hospital course: A retrospective study at a level 1 trauma center. Journal of the American College of Surgeons. 2015;1)(4):S168. doi: 10.1016/j.jamcollsurg.2015.07.401
37. Holman A, Dutta A, Gabuzda D. Long-term effects of nitrite inhalants on cardiovascular and renal outcomes in the macs cohort. Topics in Antiviral Medicine. 2014;22 (E-1):378.
38. Huber F, Merceron A, Madec Y, Gadio G, About V, Pastre A, et al. High mortality among male HIV-infected patients after prison release: ART is not enough after incarceration with HIV. PLoS ONE [Electronic Resource]. 2017;12(4):e0175740. doi:10.1371/journal.pone.0175740
39. Kertesz SG, Khodneva Y, Richman J, Tucker JA, Safford MM, Jones B, et al. Trajectories of drug use and mortality outcomes among adults followed over 18 years. Journal of General Internal Medicine. 2012;27(7):808-16. doi:10.1007/s11606-011-1975-3
40. Kucab P, Bhattacharya P. Epidemiology of Acquired Immune Deficiency Syndrome and Cerebrovascular Disease in a Post Antiretroviral Era. Journal of Stroke and Cerebrovascular Diseases. 2017;26(6):1197-203. doi:10.1016/j.jstrokecerebrovasdis.2017.01.006
41. Landerholm K, Shcherbina L, Falkmer SE, Jarhult J, Wierup N. Expression of cocaine- and amphetamine-regulated transcript is associated with worse survival in small bowel carcinoid tumors. Clinical Cancer Research. 2012;18(13):3668-76.
42. Lank PM, Crandall ML. Outcomes for older trauma patients in the emergency department screening positive for alcohol, cocaine, or marijuana use. American Journal of Drug and Alcohol Abuse. 2014;40(2):118-24. doi:10.3109/00952990.2014.880450
43. Levine M, LoVecchio F, Ruha AM, Chu G, Roque P. Influence of drug use on morbidity and mortality in heatstroke. Journal of Medical Toxicology: Official Journal of the American College of Medical Toxicology. 2012;8(3):252-7. doi:10.1007/s13181-012-0222-6
44. Lovrecic B, Semerl JS, Maremmani I, Maremmani AGI. The filing of addicted patients at addiction units is correlated with a reduction in mortality due to illicit opioids, but also to prescribed opioids and other substances of abuse. Heroin Addiction and Related Clinical Problems. 2016;18(3):15-22.
45. Mack KA. Drug-induced deaths - United States, 1999-2010. MMWR: Morbidity & Mortality Weekly Report - Supplement. 2013;62(3):161-3.
46. Marsden J, Stillwell G, Jones H, Cooper A, Eastwood B, Farrell M, et al. Does exposure to opioid substitution treatment in prison reduce the risk of death after release? A national prospective observational study in England. Addiction. 2017;112(8):1408-18. doi:10.1111/add.13779
47. Marzo JN, Rotily M, Meroueh F, Varastet M, Hunault C, Obradovic I, et al. Maintenance therapy and 3-year outcome of opioid-dependent prisoners: A prospective study in France (2003-06). Addiction. 2009;104(7):1233-40. doi:10.1111/j.1360-0443.2009.02558.x
48. Maxwell JC, Coleman JJ, Feng SY, Goto CS, Tirado CF. Cheese: An old drug in a new wrapper. Drug and Alcohol Dependence. 2012;126(1-2):161-7. doi:10.1016/j.drugalcdep.2012.05.015
49. Miro O, Galicia M, Dargan P, Dines AM, Giraudon I, Heyerdahl F, et al. Intoxication by gamma hydroxybutyrate and related analogues: Clinical characteristics and comparison between pure intoxication and that combined with other substances of abuse. Toxicology Letters. 2017;277:84-91. doi:10.1016/j.toxlet.2017.05.030
50. Mulla ZD, Wilson B, Abedin Z, Hernandez LL, Plavsic SK. Acute myocardial infarction in pregnancy: a statewide analysis. Journal of registry management. 2015;42(1):12-7.

51. Naderi N, Moriyama D, Lin J, Sazgar M, Sen-Gupta I, Mnatsakanyan L. Predictors of in-hospital mortality in status epilepticus; data from the nationwide inpatient sample database, 2008-2012. Neurology Conference: 67th American Academy of Neurology Annual Meeting, AAN. 2015;84(SUPPL. 14).
52. Naval N, Kowalski R, Chang T, Caserta F, Nyquist P, Carhuapoma J, et al. Sah score improves accuracy of hospital mortality prediction. Critical Care Medicine. 2012;1)(12):161.
53. Niclauss L, Delay D, von Segesser LK. Type A dissection in young patients. Interactive Cardiovascular and Thoracic Surgery. 2011;12(2):194-8. doi:10.1510/icvts.2010.245225
54. O'Connor AD, Padilla-Jones A, Gerkin RD, Levine M. Prevalence of Rhabdomyolysis in Sympathomimetic Toxicity: a Comparison of Stimulants. Journal of Medical Toxicology. 2015;11(2):195-200. doi:10.1007/s13181-014-0451-y
55. O'Donnell S, Geotchues A, Beavers F, Akbari C, Lowery R, Elmassry S, et al. Endovascular management of acute aortic dissections. Journal of Vascular Surgery. 2011;54(5):1283-9. doi:10.1016/j.jvs.2011.04.025
56. Ostergaard MLD, Benros ME, Toftdahl NG, Erlangsen A, Andersen JT, Nordentoft M. Association between alcohol and substance use disorders and all-cause and cause-specific mortality in schizophrenia, bipolar disorder, and unipolar depression: A nationwide, prospective, register-based study. The Lancet Psychiatry. 2015;2(9):801-8. doi:10.1016/S2215-0366(15)00207-2
57. Peles E, Linzy S, Kreek MJ, Adelson Dr M. Prospective study of QTc changes among former opiate addicts since admission to methadone maintenance treatment. Journal of Addiction Medicine. 2013;7(6):428-34. doi:10.1097/ADM.0b013e3182a8a4f2
58. Perrin-Terrin A, Pathak A, Lapeyre-Mestre M. QT interval prolongation: Prevalence, risk factors and pharmacovigilance data among methadone-treated patients in France. Fundamental and Clinical Pharmacology. 2011;25(4):503-10. doi:10.1111/j.1472-8206.2010.00871.x
59. Pfister GJ, Burkes RM, Guinn B, Steele J, Kelley RR, Wiemken TL, et al. Opioid overdose leading to intensive care unit admission: Epidemiology and outcomes. Journal of Critical Care. 2016;35:29-32. doi:10.1016/j.jcrc.2016.04.022
60. Ranney DN, Acker WB, Al-Holou SN, Ehrlichman L, Lee DS, Lewin SA, et al. Marijuana use in potential liver transplant candidates. American Journal of Transplantation. 2009;9(2):280-5. doi:10.1111/j.1600-6143.2008.02468.x
61. Rayburn RL, Pals H, Wright JD. Death, drugs, and disaster: mortality among New Orleans' homeless. Care Management Journals. 2012;13(1):8-18.
62. Ridpath A, Driver CR, Nolan ML, Karpati A, Kass D, Paone D, et al. Illnesses and deaths among persons attending an electronic dance-music festival - New York City, 2013. MMWR - Morbidity & Mortality Weekly Report. 2014;63(50):1195-8.
63. Rostami M, Mohammadi Y, Nazparvar B. Modeling spatio-temporal variations of substance abuse mortality in Iran using a log-Gaussian Cox point process. Spatial and Spatio-temporal Epidemiology. 2017;22:15-25. doi:10.1016/j.sste.2017.05.002
64. Rowe C, Santos GM, Behar E, Coffin PO. Correlates of overdose risk perception among illicit opioid users. Drug and Alcohol Dependence. 2016;159:234-9. doi:10.1016/j.drugalcdep.2015.12.018
65. Sanchez K, Chartier KG, Greer TL, Walker R, Carmody T, Rethorst CD, et al. Race and ethnicity differences among adults with stimulant use disorders in a residential treatment setting: A baseline analysis of the stride cohort. Drug and Alcohol Dependence. 2015;146:e88.
66. Sanvisens A, Fuster D, Serra I, Tor J, Tural C, Rey-Joly C, et al. Estimated liver fibrosis and its impact on all-cause mortality of HCV Monoinfected and HCV/HIV-coinfected drug users. Current HIV Research. 2011;9(4):256-62. doi:10.2174/157016211796320298
67. Schumer EM, Ising MS, Trivedi JR, Slaughter MS, Cheng A. Early Outcomes With Marginal Donor Hearts Compared With Left Ventricular Assist Device Support in Patients With Advanced Heart Failure. Annals of Thoracic Surgery. 2015;100(2):522-7. doi:10.1016/j.athoracsur.2015.02.089

68. Simpson BM, Victor D, Choi HA, Savarraj J, Bajgur S, Torres G, et al. Mortality after subarachnoid hemorrhage is associated with liver dysfunction identified by APRI and MELD score. Neurocritical Care. 2015;1):S240.
69. Skinner ML, Haggerty KP, Fleming CB, Catalano RF, Gainey RR. Opiate-Addicted parents in methadone treatment: Long-term recovery, health, and family relationships. Journal of Addictive Diseases. 2011;30(1):17-26. doi:10.1080/10550887.2010.531670
70. Soyka M, Strehle J, Rehm J, Buhringer G, Wittchen HU. Six-Year Outcome of Opioid Maintenance Treatment in Heroin-Dependent Patients: Results from a Naturalistic Study in a Nationally Representative Sample. European Addiction Research. 2017;23(2):97-105. doi:10.1159/000468518
71. Soyuncu S, Bektas F. Comparison of the scoring systems for predicting mortality in intoxicated patients hospitalized to the icu: A prospective observational study. Erciyes Tip Dergisi. 2011;33(1):029-34.
72. Tookes H, Diaz C, Li H, Khalid R, Doblecki-Lewis S. A cost analysis of hospitalizations for infections related to injection drug use at a county safety-net hospital in Miami, Florida. PLoS ONE. 2015;10 (6) (no pagination)(e0129360). doi:ARTN e0129360 10.1371/journal.pone.0129360
73. van Laere I, de Wit M, Klazinga N. Shelter-based convalescence for homeless adults in Amsterdam: a descriptive study. BMC health services research. 2009;9:208. doi:10.1186/1472-6963-9-208
74. Villa-Manzano AI, Lamas-Flores S, Mendez-Cervantes D, Villa-Manzano R, Cabrera-Pivaral CE, Rojo-Contreras W. [Motives of requirement for health care consultations and factors associated to mortality due to poisoning]. Revista medica del Instituto Mexicano del Seguro Social. 2009;47(6):647-50.
75. Warner DO, Berge K, Sun H, Harman A, Hanson A, Schroeder DR. Substance use disorder among anesthesiology residents, 1975-2009. JAMA - Journal of the American Medical Association. 2013;310(21):2289-96. doi:10.1001/jama.2013.281954
76. Westermeyer J, Lee K. Residential placement for veterans with addiction: American society of addiction medicine criteria vs. a veterans homeless program. Journal of Nervous and Mental Disease. 2013;201(7):567-71. doi:10.1097/NMD.0b013e3182982d1a

Duplicate

1. Bartolucci J, Nazzal NC, Verdugo FJ, Prieto JC, Sepulveda P, Corbalan R. [Characteristics, management, and outcomes of illicit drug consumers with acute myocardial infarction]. Revista Medica de Chile. 2016;144(1):39-46. doi:10.4067/S0034-98872016000100006
2. Calcaterra S, Glanz J, Binswanger IA. National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999-2009. Drug and Alcohol Dependence. 2013;131(3):263-70. doi:10.1016/j.drugalcdep.2012.11.018
3. Caudarella A, Dong H, Milloy MJ, Kerr T, Wood E, Hayashi K. Non-fatal overdose as a risk factor for subsequent fatal overdose among people who inject drugs. Drug and Alcohol Dependence 2016; **162**: 51-5.
4. Dias AC, Araujo MR, Laranjeira R. Evolution of drug use in a cohort of treated crack cocaine users. Revista de Saude Publica. 2011;45(5):938-48. doi:10.1590/S0034-89102011005000049
5. Dines AM, Wood DM, Yates C, Heyerdahl F, Hovda KE, Giraudon I, et al. Acute recreational drug and new psychoactive substance toxicity in Europe: 12 months data collection from the European Drug Emergencies Network (Euro-DEN). Clinical Toxicology. 2015;53(9):893-900. doi:10.3109/15563650.2015.1088157
6. Fuster D, Sanvisens A, Bolao F, et al. Cannabis as Secondary Drug Is Not Associated with a Greater Risk of Death in Patients with Opiate, Cocaine, or Alcohol Dependence. Journal of Addiction Medicine 2017; **11**(1): 34-9.

7. Hayashi K, Milloy MJ, Wood E, Dong H, Montaner JSG, Kerr T. Predictors of liver-related death among people who inject drugs in Vancouver, Canada: A 15-year prospective cohort study. Journal of the International AIDS Society. 2014;17 (no pagination)(A97). doi:Artn 19296 10.7448/Ias.17.1.19296
8. Hayden A, Hayashi K, Dong H, Milloy MJ, Kerr T, Montaner JS, et al. The impact of drug use patterns on mortality among polysubstance users in a Canadian setting: a prospective cohort study. BMC public health. 2014;14:1153. doi:Artn 1153 10.1186/1471-2458-14-1153
9. Honer WG, Cervantes-Larios A, Jones AA, Vila-Rodriguez F, Montaner JS, Tran H, et al. The Hotel Study - Clinical and Health Service Effectiveness in a Cohort of Homeless or Marginally Housed Persons. Canadian Journal of Psychiatry. 2017;62(7):482-92. doi:10.1177/0706743717693781
10. Kucab P, Bhattacharya P. The changing epidemiology of stroke in acquired immune deficiency syndrome (AIDS). Neurology Conference: 67th American Academy of Neurology Annual Meeting, AAN. 2015;84(SUPPL. 14).
11. Lank PM, Pathak M, Crandall M. Outcomes for older trauma patients with positive drug or alcohol screens in the emergency department. Annals of Emergency Medicine. 2011;1)(4):S287. doi:DOI 10.1016/j.annemergmed.2011.06.356
12. Manini AF, Vlahov D, Stimmel B, Hoffman RS. Initial ED cardiac troponin is highly predictive of drug overdose mortality. Academic Emergency Medicine. 2013;1):S70.
13. Murthy S, Shah S, Moradiya Y, Shastri A, Smirnakis S. Clinical outcomes of aneurysmal subarachnoid hemorrhage with cocaine use in the united states. Neurology Conference: 66th American Academy of Neurology Annual Meeting, AAN. 2014;82(10 SUPPL. 1).
14. Nguyen P, Kamran H, Nasir S, Chan W, Bozkurt B. No increase in mortality seen with beta-blocker treatment in heart failure patients with cocaine use. Journal of Cardiac Failure. 2015;1)(8):S120. doi:DOI 10.1016/j.cardfail.2015.06.344
15. Pagels Mardhed E, Hakansson A. Opioid maintenance treatment and mortality in opiate users leaving prison - A naturalistic follow-up study. Heroin Addiction and Related Clinical Problems. 2016;18 (3 Supplement 1):18-9.
16. Pavarin RM. Mortality Risk Among Heroin Abusers: Clients and Non-clients of Public Treatment Centers for Drug Addiction. Substance use & misuse. 2015;50(13):1690-6. doi:10.3109/10826084.2015.1027932
17. Pavarin RM, Fioritti A, Sanchini S. Mortality trends among heroin users treated between 1975 and 2013 in Northern Italy: Results of a longitudinal study. Journal of Substance Abuse Treatment. 2017;77:166-73. doi:10.1016/j.jsat.2017.02.009

Cohort defined on the basis of acute care for overdose/poisoning

1. Bhattacharya P, Taraman S, Shankar L, Chaturvedi S, Madhavan R. Clinical profiles, complications, and disability in cocaine-related ischemic stroke. Journal of Stroke and Cerebrovascular Diseases. 2011;20(5):443-9. doi:10.1016/j.jstrokecerebrovasdis.2010.02.017
2. Dean JH, Woznicki EM, O'Gara P, Montgomery DG, Trimarchi S, Myrmel T, et al. Cocaine-related aortic dissection: Lessons from the international registry of acute aortic dissection. American Journal of Medicine. 2014;127(9):878-85. doi:10.1016/j.amjmed.2014.05.005
3. Guirgis FW, Gray-Eurom K, Mayfield TL, Imbt DM, Kalynych CJ, Kraemer DF, et al. Impact of an abbreviated cardiac enzyme protocol to aid rapid discharge of patients with cocaine-associated chest pain in the clinical decision unit. Western Journal of Emergency Medicine. 2014;15(2):180-3. doi:10.5811/westjem.2013.11.19232
4. Manini AF, Stimmel B, Vlahov D, Hoffman RS. Initial emergency department cardiac troponin is highly predictive of mortality from drug overdose. Clinical Toxicology. 2013;51 (4)(4):289-90.
5. Walsh KM, Chang AM, Perrone J, McCusker CM, Shofer FS, Collin MJ, et al. Coronary computerized tomography angiography for rapid discharge of low-risk patients with cocaine-associated chest pain. Journal of Medical Toxicology. 2009;5(3):111-9.

Subpopulations that have an increased risk of mortality

Severe health presentation or procedure increasing mortality risk

1. Kayo N, Shitole S, Beheshtian A, Srinivas V, Scheuer J, Kizer J. Clinical profile, acute care and outcome of cocaine-associated ST-elevation myocardial infarction in a vulnerable urban community. Journal of the American College of Cardiology. 2014;1):A125.
2. Shitole SG, Kayo N, Srinivas V, et al. Clinical Profile, Acute Care, and Middle-Term Outcomes of Cocaine-Associated ST-Segment Elevation Myocardial Infarction in an Inner-City Community. *American Journal of Cardiology* 2016; **117**(8): 1224-30.
3. Wang Z, Lenehan B, Itshayek E, et al. Primary pyogenic infection of the spine in intravenous drug users: a prospective observational study. *Spine* 2012; **37**(8): 685-92.

Cardiovascular presentations related to cocaine exposure

1. Cunningham R, Walton MA, Weber JE, et al. One-Year Medical Outcomes and Emergency Department Recidivism After Emergency Department Observation for Cocaine-Associated Chest Pain. Annals of Emergency Medicine 2009; 53(3): 310-20. doi:10.1016/j.annemergmed.2008.07.018
2. Egbuche O, Ekechukwu I, Maduabum N, Obinwa U, Ukpaka K, Onwuanyi A. Effect of beta-blocker therapy on readmissions and mortality in heart failure patients with ongoing cocaine use. Journal of Invasive Cardiology 2017; 29 (10): E111.
3. Nguyen P, Kamran H, Nasir S, et al. Comparison of Frequency of Cardiovascular Events and Mortality in Patients With Heart Failure Using Versus Not Using Cocaine. Am J Cardiol 2017; 119(12): 2030-4. doi:10.1016/j.amjcard.2017.03.034
4. Peralta R, Yoon A, Atoui M, et al. Efficacy of cardiac computerized tomographic angiography in the evaluation of patients with cocaine-induced chest pain: A pilot randomized trial. Circulation Conference: American Heart Association's 2014; 130(Supplement 2): A18655.

HIV positive cohort

1. Campa A, Martinez SS, Sherman KE, et al. Cocaine use and liver disease are associated with all-cause mortality in the Miami adult studies in HIV (MASH) cohort Journal of Drug Abuse 2016; 2(4). doi:10.21767/2471-853X.100036
2. Nacher M, Adenis A, Hanf M, et al. Crack cocaine use increases the incidence of AIDS-defining events in French Guiana. AIDS 2009; 23(16): 2223-6. doi:10.1097/QAD.0b013e32833147c2
3. Weber E, Huber M, Battegay M, et al. Influence of noninjecting and injecting drug use on mortality, retention in the cohort, and antiretroviral therapy, in participants in the Swiss HIV Cohort Study HIV Medicine 2015; 16(3): 137-51. doi:10.1111/hiv.12184

Cocaine use not defined as regular or problematic

1. Cohen P, Sas A. Ten years of cocaine: A follow-up study of 64 cocaine users in Amsterdam. Amsterdam: Department of Human Geography, University of Amsterdam; 1993.
2. Hakansson A, Berglund M. All-cause mortality in criminal justice clients with substance use problems-A prospective follow-up study. *Drug and Alcohol Dependence* 2013; **132**(3): 499-504.
3. Jones AA, Vila-Rodriguez F, Leonova O, et al. Mortality from treatable illnesses in marginally housed adults: A prospective cohort study. *BMJ Open* 2015; **5 (8) (no pagination)**(e008876): e008876.
4. Muhuri PK, Gfroerer JC. Mortality associated with illegal drug use among adults in the United States. *The American Journal of Drug and Alcohol Abuse* 2011; **37**(3): 155-64.

Appendix J: Included studies

Table J1: List of included cohorts (*n=21*), derived from 28 publications (21 primary and 7 associated secondary publications)

Trials	Papers	Study	Citation	Primary study	Comments	% women	Age at baseline	% PWID	% regular or problematic cocaine use
1	1	Accurso, 2015[14]	Accurso AJ, Rastegar DA, Ghazarian SR, Fingerhood MI. Impact of hepatitis C status on 20-year mortality of patients with substance use disorders. *Addiction Science & Clinical Practice* 2015; **10**(20): 1-8. doi:10.1186/s13722-015-0041-6	1					100% dependent on cocaine
2	2	Arendt, 2011[15]	Arendt M, Munk-Jorgensen P, Sher L, Jensen SOW. Mortality among individuals with cannabis, cocaine, amphetamine, MDMA, and opioid use disorders: A nationwide follow-up study of Danish substance users in treatment. *Drug and Alcohol Dependence* 2011; **114**(2-3): 134-9.	1					100% dependent on cocaine
3	3	Barrio, 2013[9]	Barrio G, Molist G, de la Fuente L, et al. Mortality in a cohort of young primary cocaine users: Controlling the effect of the riskiest drug-use behaviors. *Addictive Behaviors* 2013; **38**(3): 1601-4. doi:10.1016/j.addbeh.2012.10.007	1					100% report primary drug used as cocaine
4	4	Bohnert, 2017[16]	Bohnert KM, Ilgen MA, Louzon S, McCarthy JF, Katz IR. Substance use disorders and the risk of suicide mortality among men and women in the US Veterans Health Administration. *Addiction* 2017; **112**(7): 1193-201. doi:10.1111/add.13774	1		3.87%			100% dependent on cocaine
5	5	Callaghan, 2013[10]	Callaghan RC, Gatley JM, Veldhuizen S, Lev-Ran S, Mann R, Asbridge M. Alcohol- or drug-use disorders and motor vehicle accident mortality: a retrospective cohort study. *Accident; analysis and prevention* 2013; **53**: 149-55. doi:10.1016/j.aap.2013.01.008	1		46%			100% dependent on cocaine
	6	Callaghan, 2012[17]	Callaghan RC, Cunningham JK, Verdichevski M, Sykes J, Jaffer SR, Kish SJ. All-cause mortality among individuals with disorders related to the use of methamphetamine: A comparative cohort study. *Drug and Alcohol Dependence* 2012; **125**(3): 290-4. doi:10.1016/j.drugalcdep.2012.03.004	0	Secondary paper of Callaghan, 2013 – same recruitment method in similar timeframe resulting in potentially both including the same participants				100% dependent on cocaine
6	7	de la Fuente, 2014[18]	de la Fuente L, Molist G, Espelt A, et al. Mortality risk factors and excess mortality in a cohort of cocaine users admitted to drug treatment in Spain. *Journal of Substance Abuse Treatment* 2014; **46**(2): 219-26. doi:10.1016/j.jsat.2013.07.001	1		17.9%	31.0 (mean)	23.1%	100% dependent on cocaine
	8	Brugal, 2016[19]	Brugal M, Molist G, Sarasa-Renedo A, et al. Assessing gender disparities in excess mortality of heroin or cocaine users compared to the general population. *International Journal of Drug Policy* 2016; **38**: 36-42. doi:10.1016/j.drugpo.2016.10.009	0	Secondary paper of de la Fuente, 2014 - same recruitment method within similar timeframe resulting in same participants being double counted				100% dependent on cocaine
	9	Molist, 2018[20]	Molist G, Brugal MT, Barrio G, et al. Effect of ageing and time since first heroin and cocaine use on mortality from external and natural causes in a Spanish cohort of drug users. *International Journal of Drug Policy* 2018; **53**: 8-16. doi:10.1016/j.drugpo.2017.11.011	0	Secondary paper of de la Fuente, 2014 – same recruitment method within similar timeframe resulting in same participants being double counted				100% dependent on cocaine
	10	Colell, 2018[21]	Colell E, Domingo-Salvany A, Espelt A, Pares-Badell O, Brugal MT. Differences in mortality in a cohort of cocaine use disorder patients with concurrent alcohol or opiates disorder. *Addiction* 2018; **113**(6): 1045-55. doi:10.1111/add.14165	0	Secondary paper of de la Fuente, 2014 – same recruitment method within similar timeframe resulting in same participants being double counted				100% dependent on cocaine
7	11	Dias, 2011[22]	Dias AC, Araujo MR, Dunn J, Sesso RC, de Castro V, Laranjeira R. Mortality rate among crack/cocaine-dependent patients: A 12-year prospective cohort study conducted in Brazil. *Journal of Substance Abuse Treatment* 2011; **41**(3): 273-8. doi:10.1016/j.jsat.2011.03.008	1		11.45%			100% dependent on cocaine
8	12	Gossop, 2002[23]	Gossop M, Stewart D, Treacy S, Marsden J. A prospective study of mortality among drug misusers during a 4-year period after seeking treatment. *Addiction* 2002; **97**(1): 39-47. doi:10.1046/j.1360-0443.2002.00079.x	1					100% report regular use of cocaine
9	13	Hayashi, 2016[11]	Hayashi K, Dong H, Marshall BD, et al. Sex-Based Differences in Rates, Causes, and Predictors of Death Among Injection Drug Users in Vancouver, Canada. *American Journal of Epidemiology* 2016; **183**(6): 544-52. doi:10.1093/aje/kwv207	1				100%	100% report injecting cocaine in past 6 months

	14	Tyndall, 2001[24]	Tyndall MW, Craib KJP, Currie S, Li K, O'Shaughnessy MV, Schechter MT. Impact of HIV infection of mortality in a cohort of injection drug users. *Journal of Acquired Immune Deficiency Syndrome* 2001; **28**(4): 351-7. doi:10.1097/00126334-200112010-00008	0	Secondary paper of Hayashi, 2016 – both papers utilised same database of individuals (VIDUS) with overlapping recruitment periods resulting in duplicate data within the 2 papers				100% report injecting cocaine in past 6 months
10	15	Hser, 2012[25]	Hser YI, Kagihara J, Huang D, Evans E, Messina N. Mortality among substance-using mothers in California: a 10-year prospective study. *Addiction* 2012; **107**(1): 215-22. doi:10.1111/j.1360-0443.2011.03613.x	1		100%			100% dependent on cocaine
11	16	Lopez, 2004[12]	Lopez D, Martineau H, Palle C. Mortality of individuals arrested for heroin, cocaine or crack use, 2004.	1					100% arrested for using cocaine
12	17	Markota, 2016[26]	Markota M, Croarkin PE, Bobo WV. Increased 5-year all-cause mortality in youth with positive urine cocaine drug screens. *Journal of the American Academy of Child and Adolescent Psychiatry* 2016; **55 (10 Supplement 1)**: S148. doi:10.1016/j.jaac.2016.09.151	1		40%			100% tested positive for cocaine use
13	18	Martell, 2009[27]	Martell BA, Orson FM, Poling J, et al. Cocaine vaccine for the treatment of cocaine dependence in methadone-maintained patients: A randomized, double-blind, placebo-controlled efficacy trial. *Archives of General Psychiatry* 2009; **66**(10): 1116-23. doi:10.1001/archgenpsychiatry.2009.128	1		33.3%			100% dependent on cocaine
14	19	Nielsen, 2011[28]	Nielsen SF, Hjorthoj CR, Erlangsen A, Nordentoft M. Psychiatric disorders and mortality among people in homeless shelters in Denmark: A nationwide register-based cohort study. *The Lancet* 2011; **377**(9784): 2205-14. doi:10.1016/S0140-6736(11)60747-2	1		20.95%			100% dependent on cocaine
15	20	O'Driscoll, 2001[29]	O'Driscoll PT, McGough J, Hagan H, Thiede H, Critchlow C, Alexander ER. Predictors of accidental fatal drug overdose among a cohort of injection drug users. *American Journal of Public Health* 2001; **91**(6): 984-7.	1				71.48%	100% reported primary drug injected consisted of cocaine
16	21	Pavarin, 2017[30]	Pavarin RM, Fioritti A. Mortality Trends among Cocaine Users Treated between 1989 and 2013 in Northern Italy: Results of a Longitudinal Study. *Journal of Psychoactive Drugs* 2017; **50**(1): 72-80. doi:10.1080/02791072.2017.1365976	1		12.2%	32.8	15.6%	100% dependent on cocaine
	22	Pavarin, 2008[31]	Pavarin RM. Cocaine consumption and death risk: A follow-up study on 347 cocaine addicts in the metropolitan area of Bologna. *Annali-Istituto Superiore di Sanita* 2008; **44**(1): 91-8.	0	Secondary paper of Pavarin, 2017 – same recruitment method in similar timeframes leading to potential overlap of participants between papers				100% dependent on cocaine
	23	Pavarin, 2013[32]	Pavarin RM. Mortality risk for cocaine abusers in relation to heroin use: A follow-up study. *Substance Use & Misuse* 2013; **48**(9): 702-10. doi:10.3109/10826084.2013.786731	0	Secondary paper of Pavarin, 2017 – same recruitment method in similar timeframes leading to potential overlap of participants between papers				100% dependent on cocaine
17	24	Ryb, 2009[33]	Ryb GE, Cooper CC, Dischinger PC, Kufera JA, Auman KM, Soderstrom CA. Suicides, homicides, and unintentional injury deaths after trauma center discharge: Cocaine use as a risk factor. *Journal of Trauma - Injury, Infection and Critical Care* 2009; **67**(3): 490-6. doi:10.1097/TA.0b013e3181b84430	1		16%			100% tested positive for cocaine use
18	25	Sanvisens, 2014[13]	Sanvisens A, Vallecillo G, Bolao F, et al. Temporal trends in the survival of drug and alcohol abusers according to the primary drug of admission to treatment in Spain. *Drug and Alcohol Dependence* 2014; **136**(1): 115-20. doi:10.1016/j.drugalcdep.2013.12.022	1		26.6%	32	65.8%	100% dependent on cocaine
19	26	van Haastrecht, 1996[34]	van Haastrecht HJA, van Ameijden EJC, van den Hoek JAR, Mientjes GHC, Bax JS, Coutinho RA. Predictors of mortality in the Amsterdam cohort of human immunodeficiency virus (HIV)-positive and HIV-negative drug users. *American Journal of Epidemiology* 1996; **143**(4): 380-91. doi:10.1093/oxfordjournals.aje.a008752	1		39.56%		77%	100% reported primary drug injected consisted of cocaine
20	27	Vlahov, 2008[35]	Vlahov D, Wang C, Ompad D, et al. Mortality risk among recent-onset injection drug users in five U.S. cities. *Substance Use & Misuse* 2008; **43**(3-4): 413-28. doi:10.1080/10826080701203013	1				100%	100% reported primary drug injected consisted of cocaine
21	28	Wang, 2005[36]	Wang C, Vlahov D, Galai N, et al. The effect of HIV infection on overdose mortality. *AIDS* 2005; **19**(9): 935-42. doi:10.1097/01.aids.0000171407.30866.22	1		48.84%		100%	100% reported primary drug injected consisted of cocaine

Table J2. Mortality in included studies

Study (Author, ref)	N	PY	All deaths				Drug-related[d]				Accidental injury				Suicide				Homicide				Cardiovascular				AIDS-related			
			N	CMR (95%CI)	SMR (95%CI)	RR (95%CI)	N	CMR (95%CI)	SMR (95%CI)	RR (95%CI)	N	CMR (95%CI)	SMR (95%CI)	RR (95%CI)	N	CMR (95%CI)	SMR (95%CI)	RR (95%CI)	N	CMR (95%CI)	SMR (95%CI)	RR (95%CI)	N	CMR (95%CI)	SMR (95%CI)	RR (95%CI)	N	CMR (95%CI)	SMR (95%CI)	RR (95%CI)
Accurso, 2015[14]	315	5,780*	52	0.90 (0.69-1.18)	2.11[b] (1.61-2.77)	2.12 (1.66-2.72)																								
Arendt, 2011[15]	838	2,571.43*	18	0.70 (0.44-1.11)	6.40 (3.90-10.00)	6.44 (3.91-10.09)																								
Barrio, 2013[9]	714	3,922	9	0.23 (0.12-0.44)	4.70 (2.40-9.00)	4.79 (2.42-9.40)	3	0.08 (0.02-0.24)	30.58[b] (9.86-94.82)	36.23 (10.35-187.57)					1	0.03 (0.00-0.18)	4.19[b] (0.59-29.75)	4.26 (4.05-4.49)									2	0.05 (0.01-0.20)	47.28 (11.83-189.07)	
Bohnert, 2017[16]	83,808														231	0.05 (0.04-0.06)	3.06[b] (2.69-3.48)	3.10 (3.07-3.11)												
Callaghan, 2013[10]	48,949	395,738	4,356	1.10 (1.07-1.13)	2.96[a] (2.87-3.05)	3.00[a] (2.90-3.09)					113	0.03 (0.02-0.03)	3.80 (2.30-5.30)	3.87 (2.32-5.45)																
de la Fuente, 2014[18]	11,905	65,849.1*	349	0.53 (0.48-0.59)	4.90 (4.40-5.40)	4.97 (4.45-5.49)	117[a]	0.18[a] (0.17-0.18)	66.70[a] (57.97-76.75)	86.86[a] (72.58-104.79)	45[a]	0.07[a] (0.07-0.07)	8.51[a] (6.74-10.50)	8.74[a] (6.88-10.86)	34[a]	0.05[a] (0.05-0.05)	14.86[a] (11.21-19.33)	15.62[a] (11.63-20.67)	5[a]	0.01[a] (0.01-0.01)	6.42[a] (3.43-10.88)	6.54[a] (3.46-11.27)	45[a]	0.07[a] (0.07-0.07)	2.97[a] (2.35-3.67)	2.99[a] (2.36-3.70)	4[a]	0.02[a] (0.01-0.04)	2.85[a,b] (1.07-7.73)	
Dias, 2011[22]	131	1,181.62*	27	2.28 (1.57-3.33)	14.75 (9.92-21.17)	15.55 (10.26-22.89)	3	0.25 (0.08-0.79)	48.79[b] (15.74-151.29)	59.39 (16.65-344.71)	1	0.08 (0.01-0.60)	1.43[b] (0.20-10.17)	1.43 (0.20-10.53)					16	1.35 (0.83-2.21)	24.39[b] (14.94-39.81)	26.72 (15.76-46.56)					6	0.51 (0.23-1.13)	38.12[b] (17.13-84.86)	
Gossop, 2002[23]	227						9	0.97 (0.51-1.87)	141.88[b] (73.82-272.67)																					
Hayashi, 2016[11]	1,719	11,748.6	392	3.34 (3.02-3.68)	14.05[b] (12.72-15.51)	14.64 (10.39-20.75)	54[a]	2.07 (1.19-3.59)	352.41[b] (269.91-460.14)	604.26[a] (395.99-1011.87)					7[a]	0.27[a] (0.22-0.33)	15.12[a,b] (7.21-31.71)	16.77 (13.48-20.98)					6[a]	0.23[a] (0.19-0.28)	0.11[a,b] (0.05-0.24)	0.11[a] (0.05-0.24)	30[a]	1.15[a] (0.76-1.73)		
Hser, 2012[25]	511	5,471.48*	27	0.49 (0.34-0.72)	1.96[b] (1.35-2.86)	1.97 (1.35-2.89)																								
Lopez, 2004[12]	2,212	11,496	80	0.70 (0.56-0.87)	2.09[b] (1.68-2.61)	2.10 (1.80-2.44)																								
Markota, 2016[26]	63	307.5*	3	0.98 (0.31-3.02)	2.32[b] (0.75-7.18)	2.33 (0.77-7.24)					1	0.33 (0.05-2.31)	29.49[b] (4.15-209.33)		1	0.33 (0.05-2.31)	18.20[b] (2.56-129.22)	20.21 (10.13-42.69)												
Martell, 2009[27]	115	57.5*	0	-	-	-																								
Nielsen, 2011[28]	525	5,361.5*	75	1.40 (1.12-1.75)	3.98[b] (3.17-4.99)	3.99 (2.90-5.48)																								
O'Driscoll, 2001[29]	761	2,092.32*	25	1.50 (0.89-2.54)	5.39[b] (3.19-9.10)	5.56 (2.48-12.79)	30	0.99 (0.69-1.41)	136.12[b] (95.17-194.69)	136.12 (95.68-193.66)																				
Pavarin, 2017[30]	678	4,752.85*	25	0.53 (0.36-0.78)	5.21 (3.52-7.71)	6.30 (4.63-8.60)	3	0.06 (0.02-0.20)	25.41 (8.20-78.78)	26.63 (8.31-92.19)	6	0.13 (0.06-0.28)	9.93 (4.46-22.09)	10.10 (4.49-23.00)	4	0.08 (0.03-0.22)	8.33 (3.13-22.19)	8.45 (3.14-23.11)	0	-	-	-	0	-	-	-	1	0.02 (0.00-0.15)	4.98 (0.70-35.34)	

Study (Author, ref)	N	PY	All deaths				Drug-related[d]				Accidental injury				Suicide				Homicide				Cardiovascular				AIDS-related			
Ryb, 2009[33]	2,451	15,931.5*									32	0.20 (0.14-0.28)	5.72[b] (4.04-8.08)	5.92 (4.13-8.51)	5	0.03 (0.01-0.08)	1.86[b] (0.77-4.46)	1.87 (1.82-1.92)	12	0.08 (0.04-0.13)	5.13[b] (2.91-9.04)	5.29 (2.95-9.58)								
Sanvisens, 2014[13]	2,451	7,155	202	2.80 (2.50-3.20)	6.12[b] (5.47-7.00)	6.21 (5.53-7.11)																	9	0.13 (0.10-0.24)	16.29[b] (8.48-31.31)	16.96 (8.64-33.97)	59	0.82 (0.64-1.06)	30.28[b] (23.46-39.08)	
van Haastrecht, 1996[34]		194	9	4.64 (2.41-8.92)	84.93[b] (44.19-163.24)																									
Vlahov, 2008[35]	102	485.7	3	0.62 (0.20-1.92)	5.48[b] (1.77-17.00)	5.72 (2.77-12.15)																								
Wang, 2005[36]	518	3727	175	4.69 (4.03-5.45)	13.02[b] (11.19-15.13)	14.09 (11.96-16.61)	29	0.78 (0.54-1.12)	100.12[b] (69.57-144.07)	267.11 (142.16-790.65)					2	0.05 (0.01-0.21)	3.15[b] (0.79-12.58)	3.19 (2.96-3.44)					7	0.19 (0.09-0.39)	1.95 (0.93-4.09)	1.96 (0.93-4.17)	62	1.66 (1.30-2.13)	63.87[b] (49.79-81.92)	

* PYFU was calculated using formula in **Appendix H**; [a] Information from secondary paper was used; [b] SMR was inputted using GBD 2017 estimates (see **Appendix H** for more information); [c] Insufficient data was reported to estimate confidence intervals.
[d]'Drug-related': note that estimates could include poisoning deaths, deaths attributed to mental and behavioural disorders due to psychoactive substance use, and deaths from other causes that were thought to be drug-related.

Table J3. ICD codes used to identify each cause-specific death

Study (Author,ref)	Drug-related	Suicide	Accidental Injury	Cardiovascular disease	Homicide	AIDS-related	Cancer	Respiratory disease
Barrio, 2013[9]	-	-	-	-	-	-	-	-
Bohnert, 2017[16]	-	ICD 10: X60-84, Y87.0	-	-	-	-	-	-
Brugal, 2016[19a]	ICD 9: 291, 292, 303-305, E850-869, E929.2, E980, 427.5[b], 514[b], 518.4[b], 780-799[b], 980[b]; ICD 10: F10-F19, F55, X40-X49, Y10-Y19, I46[b], J81[b], J96[b], R00-R74[b], R76-R99[b]	-	-	-	-	-	-	-
Callaghan, 2013[10]	-	-	ICD-9 810–825 (with a 4th digit of "0" or "2"); ICD-10 V20-29 (3rd digit of "0" or "4"), V30-79 (3rd digit of "0" or "5"), and V83-86 (3rd digit of "0" or "5")	-	-	-	-	-
Colell, 2018[21a]	-	-	-	ICD 10: J81, J96, J960, J969, J13, J18, J189, 496, J09, J209, J439, J441, J449, J841, J850, J90, J988	-	ICD 9: 279.5; ICD10: B20, B200, B202, B203, B205, B206, B207, B208, B209, B21, B212, B213, B218, B220, B222, B227, B238, B24	-	-
Dias, 2011[22]	-	-	-	-	-	-	-	-
Gossop, 2002[23]	-	-	-	-	-	-	-	-
Markota, 2016[26]	-	-	-	-	-	-	-	-
Molist, 2018[20a]	ICD 9: 291, 292, 303-305, 427.5[b], 514[b], 518.4[b], 780-799[b], 980.0[b], E850-869, E929.2, E980; ICD 10: F10-F19, F55, I46[b], J81[b], J96[b], R00-R74[b], R76-R99[b], X40-X49, Y10-Y19, Y90-Y91	ICD 9: E950-E959; ICD 10: X60-X84, Y87.0	ICD 9: E800-E949, E980-E989; ICD 10: V01-X59, Y10-Y34, Y40-Y86, Y87.2, Y88, Y89.9	ICD 9: 390-459; ICD 10: I00-I99	ICD 9: E960-E979, E990-E999; ICD 10: X85-Y09, Y35-Y36, Y87.1, Y89.0-Y89.1		ICD 9: 140-239; ICD 10: C00-D49	
O'Driscoll, 2001[29]	-	-	-	-	-	-	-	-
Pavarin, 2017[30]	-	-	-	-	-	-	-	-
Ryb, 2009[33]	-	-	-	-	-	-	-	-
Sanvisens, 2014[13]	-	-	-	-	-	ICD-9: 279.5, 795.8; ICD-10: B20–B24, R75	ICD-9: 140–154, 156–208, 273.3; ICD10: C00–C21, C23–C97, D00–D09, D37–D48	-
Tyndall, 2001[24c]	-	-	-	-	-	-	-	-
Wang, 2005[36]	-	-	-	-	-	-	-	-

[a] Studies were associated secondary papers of cohort presented in de la Fuente, 2014[18]; [b] Codes included as overdose deaths because in Madrid information from the forensic and toxicological register could not be consulted to correct the underlying cause of death, and Barcelona consultation had shown that such codes contained mostly overdose deaths. [c] Study was associated secondary paper of cohort presented in Hayashi, 2016[11]; -: no ICD codes reported.

Appendix K: Relative risk results

Figure K1. Pooled estimates, derived from random effects meta-analysis, of all-cause mortality relative risk among people with regular or problematic use of cocaine, overall and by region.

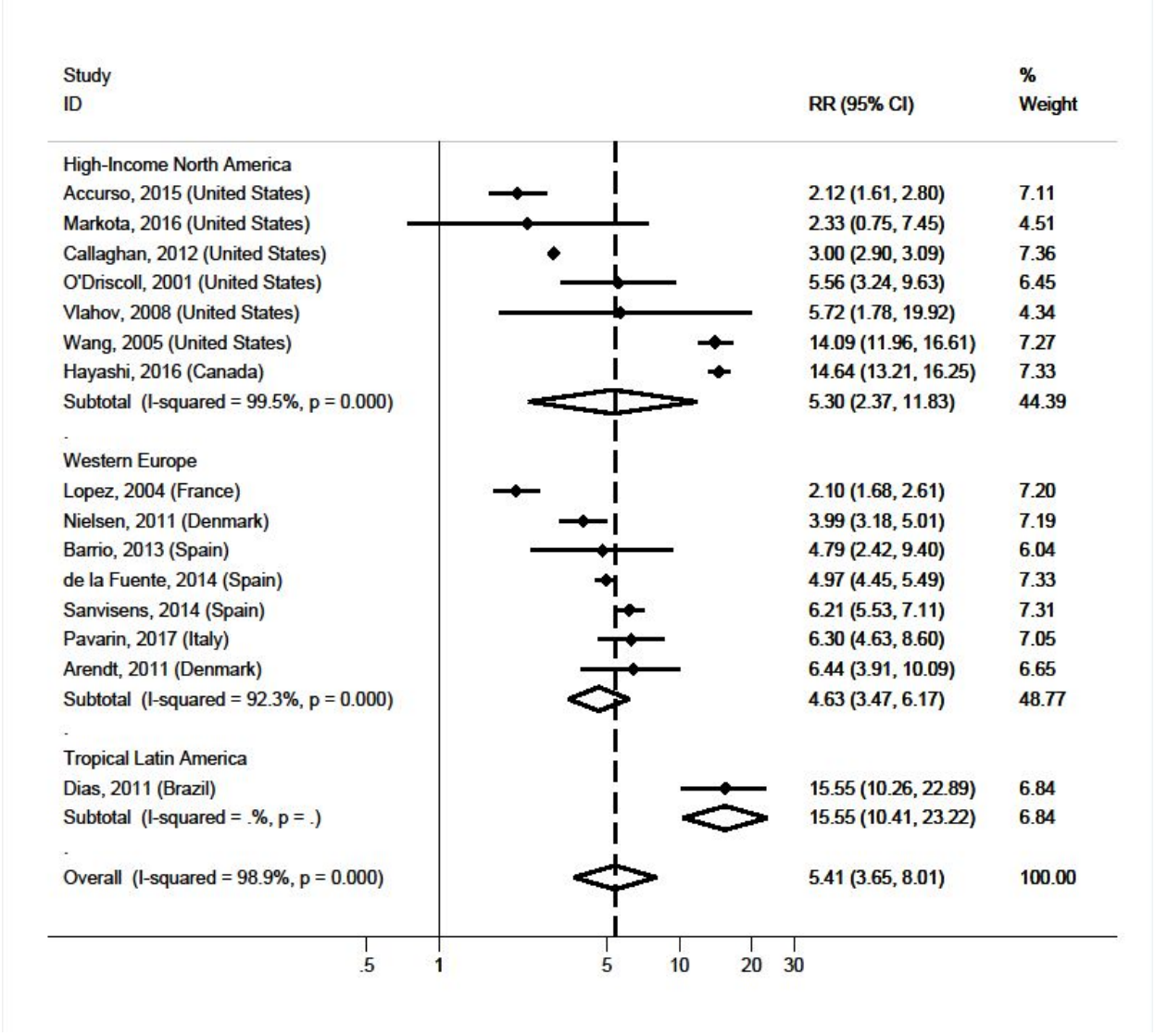


Figure K2. Forest plots of cause-specific mortality relative risk among people with regular or problematic use of cocaine.

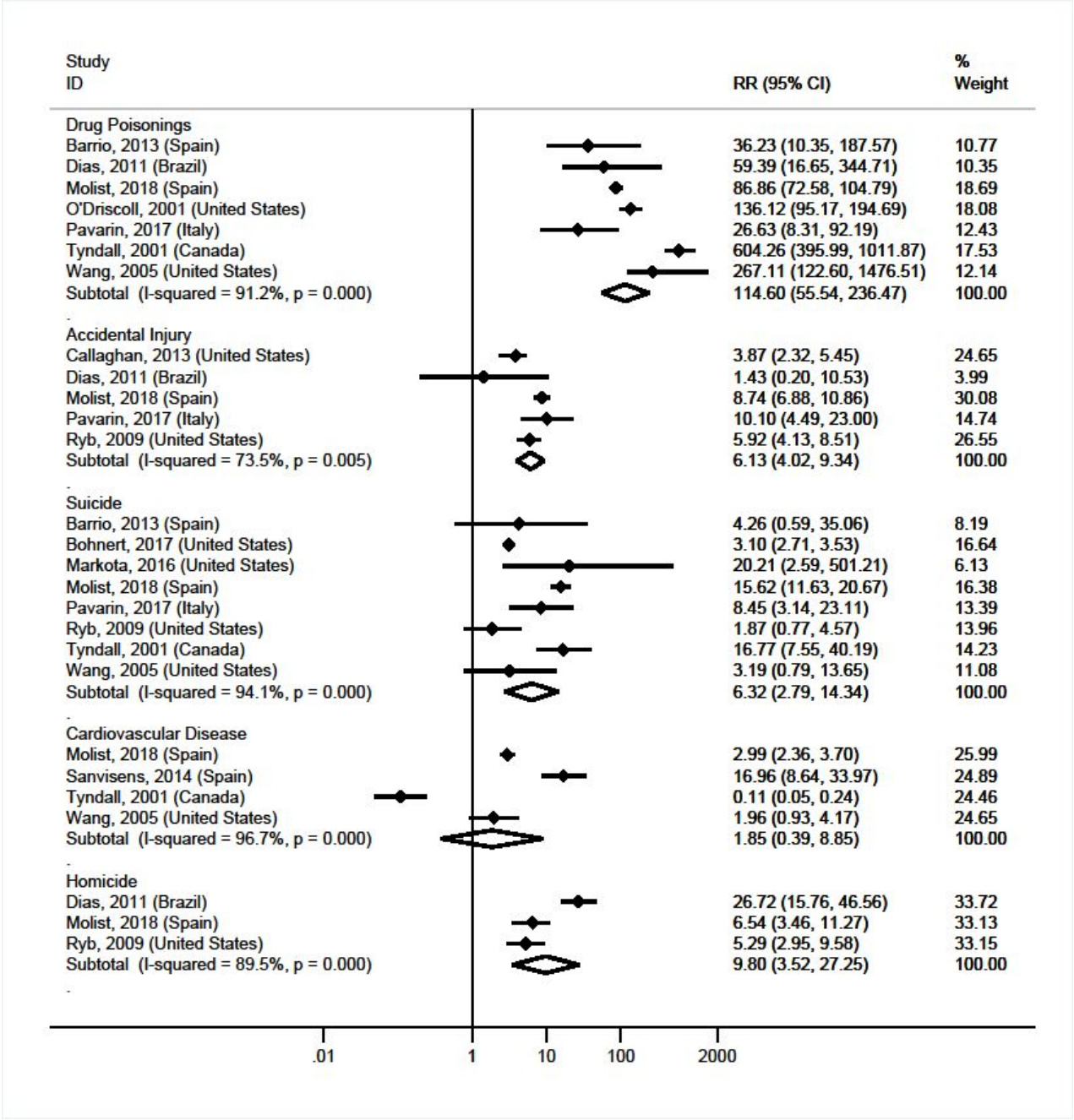


Table K1. Summary of pooled estimated relative risks of mortality among people with regular or problematic use of cocaine

	Pooled mortality relative risk (95%CI)	I^2	References
All-cause mortality	**5.41 (3.65-8.01)**	**98.9%**	**9,11-15,17,18,22,26,28-30,35,36**
Women	5.24 (3.25-8.44)	95.2%	15,17,18,25,28,31
Men	3.44 (2.86-4.15)	74.3%	15,17,18,26,28,31
GBD Region			
High-income North America	5.35 (2.80-10.25)	98.4%	11,14,17,26,29,35,36
Western Europe	4.64 (3.24-6.63)	95.4%	9,12,13,15,18,28,30
Tropical Latin America	15.55 (10.26-22.89)	-	22
Cause-specific mortality			
Drug-related[a]	114.60 (55.54-236.47)	91.2%	9,20,22,24,29,30,36
Accidental injury	6.13 (4.02-9.34)	73.5%	10,20,22,26,30,33
Suicide	6.32 (2.79-14.34)	94.1%	9,16,20,24,26,30,33,36
Cardiovascular disease	1.85 (0.39-8.85)	96.7%	13,20,24,36
Homicide	9.80 (3.52-27.25)	89.5%	20,22,33
AIDS-related	13.54 (3.78-48.56)	88.2%	13,21,22,30
Cancer	1.49 (0.70-3.18)	85.2%	13,20,24,30,36
Liver-related	3.39 (0.50-23.02)	92.5%	13,21,22
Cerebrovascular disease	-	-	-
Digestive disease	-	-	-
Nervous system	-	-	-
Respiratory disease	-	-	-

Note. [a] 'Drug-related': note that estimates could include poisoning deaths, deaths attributed to mental and behavioural disorders due to psychoactive substance use, and deaths from other causes that were thought to be drug-related.

Appendix L: Supplementary results

Table L1. Summary of pooled results using only study-reported CMRs (i.e. not including imputed CMR estimates) among people with regular or problematic use of cocaine

	No. studies	No. people	Pooled crude mortality rate (95%CI)	I^2	References
All-cause mortality	**10**	**67,159**	**1.25 (0.81-1.94)**	**99.1%**	9-13,15,18,22,30,34-36
Women[a]	4	24,596[b]	0.67 (0.56-0.81)	44.6%	10,15,18,32
Men	4	36,588[b]	0.70 (0.33-1.45)	99.0%	10,15,18,32
GBD Region					
High-income North America	4	51,288	1.98 (0.83-4.71)	99.6%	10,11,35,36
Western Europe	7	17,292[c]	0.88 (0.42, 1.85)	98.7%	9,12,13,15,18,30,34t
Tropical Latin America	1	131	2.29 (1.57-3.33)	-	22
Cause-specific mortality					
Drug-related[d]	3	12,750	0.10 (0.05-0.19)	52.5%	9,19,22
Accidental injury	3	60,985	0.05 (0.02-0.11)	92.1%	10,20,22
Suicide	2	12,619	0.05 (0.04-0.07)	0.0%	9,20
Cardiovascular disease	2	12,850	0.09 (0.05-0.15)	63.2%	13,20
Homicide	2	12,036	0.10 (0.00-16.41)	99.0%	20,22
AIDS-related	4	5,380	0.14 (0.02-0.88)	95.7%	9,13,21,22
Respiratory disease	2	4,304	0.06 (0.04-0.09)	0.0%	9,21
Cancer	2	12,850	0.06 (0.05-0.08)	0.0%	13,20
Digestive disease	1	11,905	0.03 (0.02-0.05)	-	20

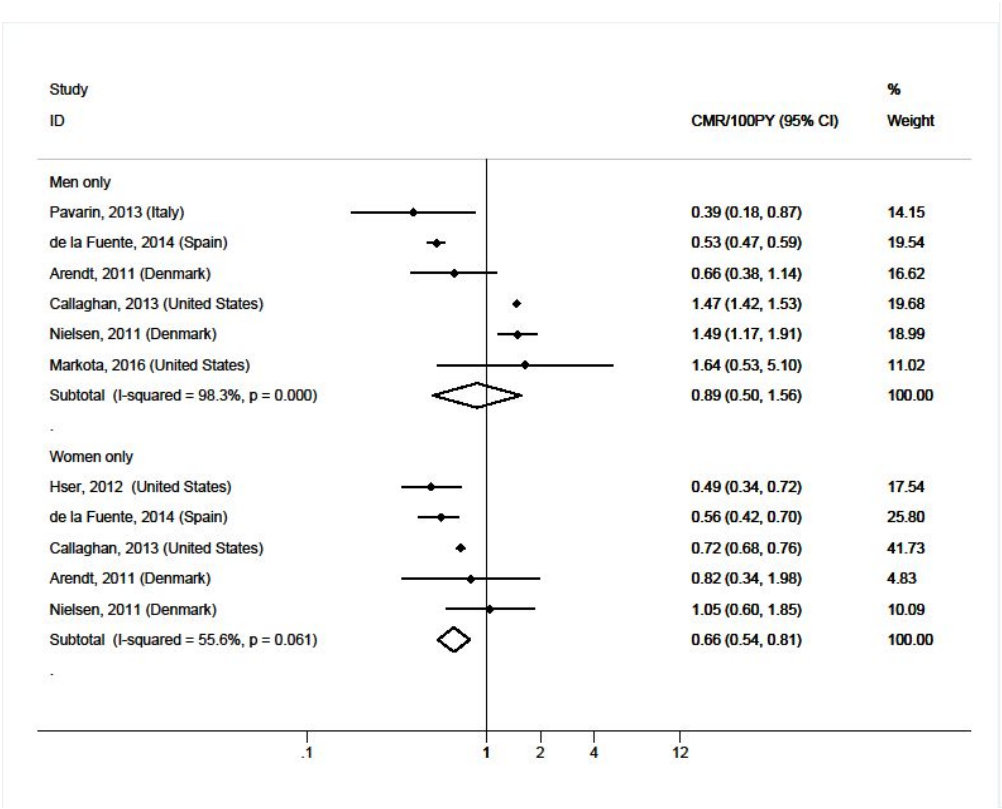
[a] Pavarin, 2013 included, but no women died. [b] Except for Arendt, 2011, all studies reported the N of cocaine-using participants [c] Except for van Haastrecht, 1996, all studies reported the N of cocaine-using participants. [d] 'Drug related': note that estimates could include poisoning deaths, deaths attributed to mental and behavioural disorders due to psychoactive substance use, and deaths from other causes that were thought to be drug-related.

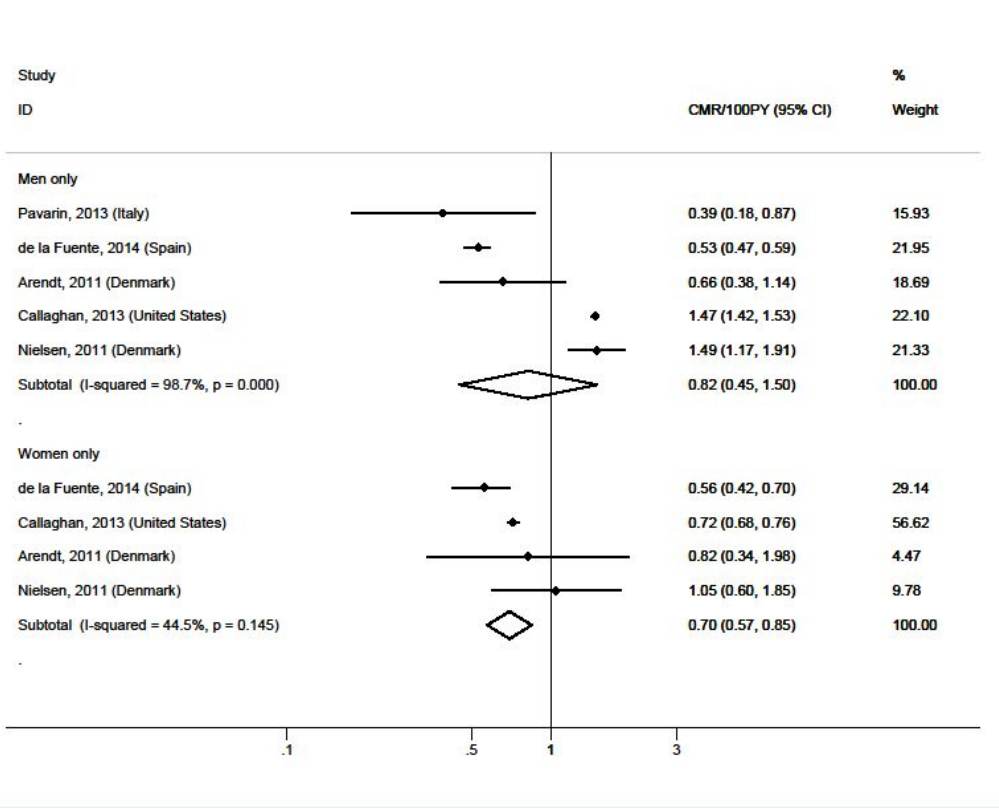
Table L2. Summary of pooled results using only study-reported SMRs (i.e. not including imputed SMR estimates) among people with regular or problematic use of cocaine

	No. studies	No. people	Pooled standardised mortality ratio (95%CI)	I^2	References
All-cause mortality	**7**	**63,431**	**5.58 (3.90-7.99)**	**96.6%**	**9,15,17,18,22,30,37**
Women	3	24,538[a]	7.00 (3.12-15.68)	96.7%	15,17,18
Men	4	36,603[a]	3.41 (2.74-4.23)	84.3%	15,17,18,31
GBD Region					
High-income North America	2	49,165	3.94 (2.11-7.35)	89.3%	17,37
Western Europe	4	14,135	4.97 (4.51-5.47)	0.0%	9,15,18,30
Tropical Latin America	1	131	14.75 (10.10-21.55)	-	22
Cause-specific mortality					
Drug-related[b]	2	12,583	44.37 (37.28-52.81)	0.0%	20,30
Accidental injury	3	61,532	5.01 (3.71-6.77)	29.9%	10,20,30
Suicide	2	12,583	9.25 (6.73-12.73)	0.0%	20,30
Cardiovascular disease	2	12,583	2.62 (1.21-5.68)	66.8%	20,30
Homicide	1	11,905	4.17 (1.69-10.25)	-	20
AIDS-related	1	678	4.98 (0.70-35.34)	-	30
Respiratory disease	1	678	24.12 (6.03-96.43)	-	30
Cancer	2	12,583	1.10 (0.61-1.98)		20,30
Digestive disease	1	11,905	1.90 (1.20-2.89)	-	20

[a] Except for Arendt, 2011, all studies reported the N of cocaine-using participants. [b] 'Drug related': note that estimates could include poisoning deaths, deaths attributed to mental and behavioural disorders due to psychoactive substance use, and deaths from other causes that were thought to be drug-related.

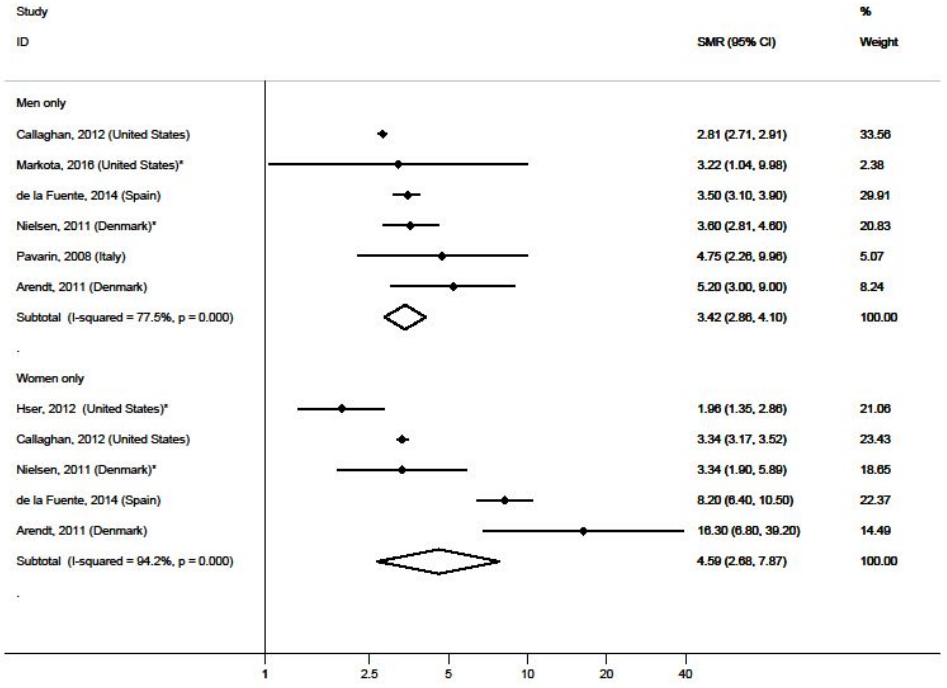
Figure L1. Pooled estimates, derived from random effects meta-analysis, for all-cause CMR by gender (men only vs. women only) per 100 person-years with studies that reported deaths by either gender (left) or both genders (right).

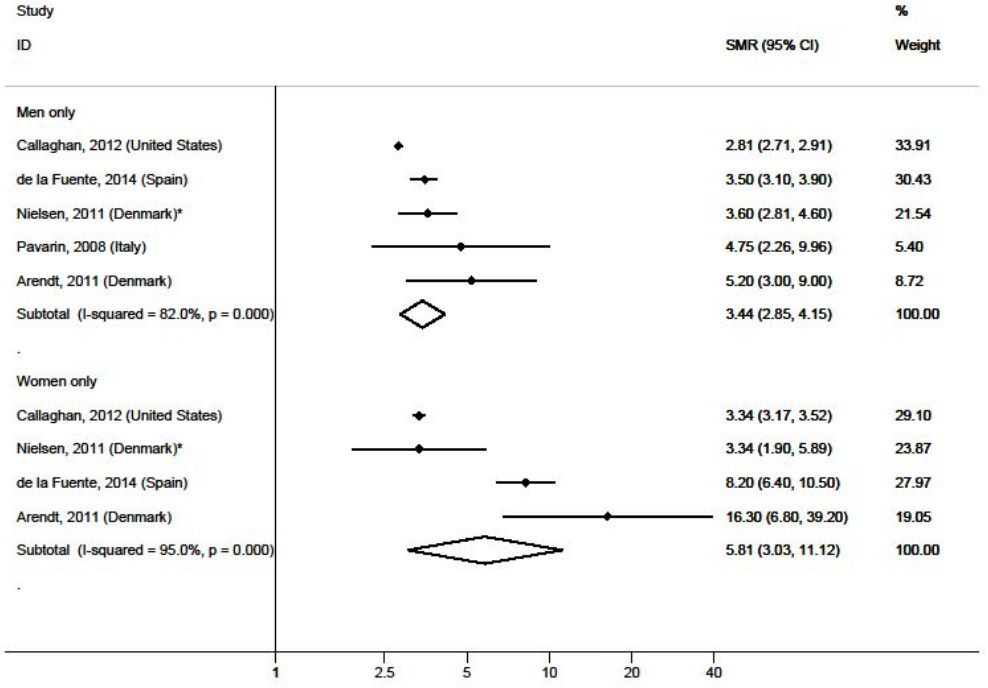




Note: Pavarin, 2013[32] reported no deaths among women and therefore not included in pooled estimate.

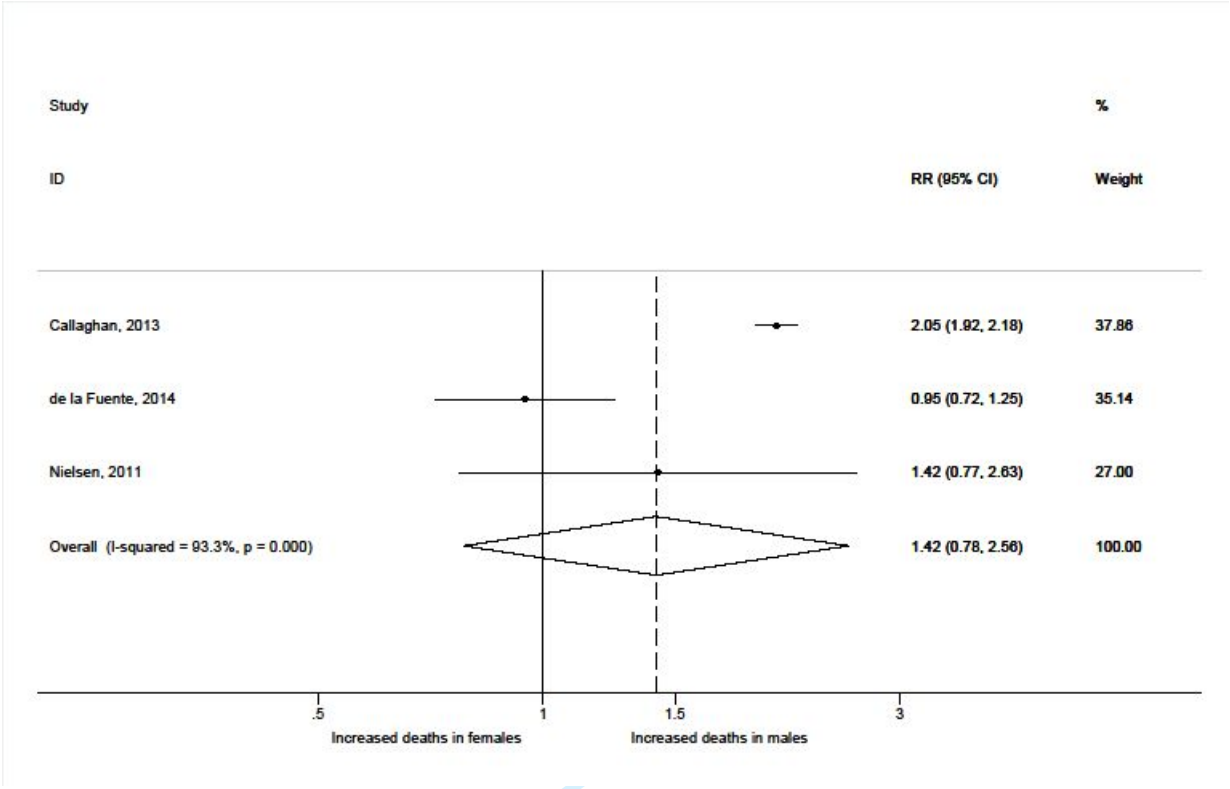
Figure L2. Pooled estimates, derived from random effects meta-analysis, for all-cause SMR by gender (men only vs. women only) per 100 person-years with studies that reported deaths by either gender (left) or both genders (right).





Note: Pavarin, 2008[31] reported no deaths among women and therefore not included in pooled estimate.

Figure L3. Forest plot displaying the pooled within-study relative risk of studies reporting all-cause crude mortality rates for men v. women (ref) (top) and older people v. younger people (ref) (bottom)



Note: Arendt, 2011[15] was not included in the gender within-study relative risk analysis as they did not report number of deaths within men and women

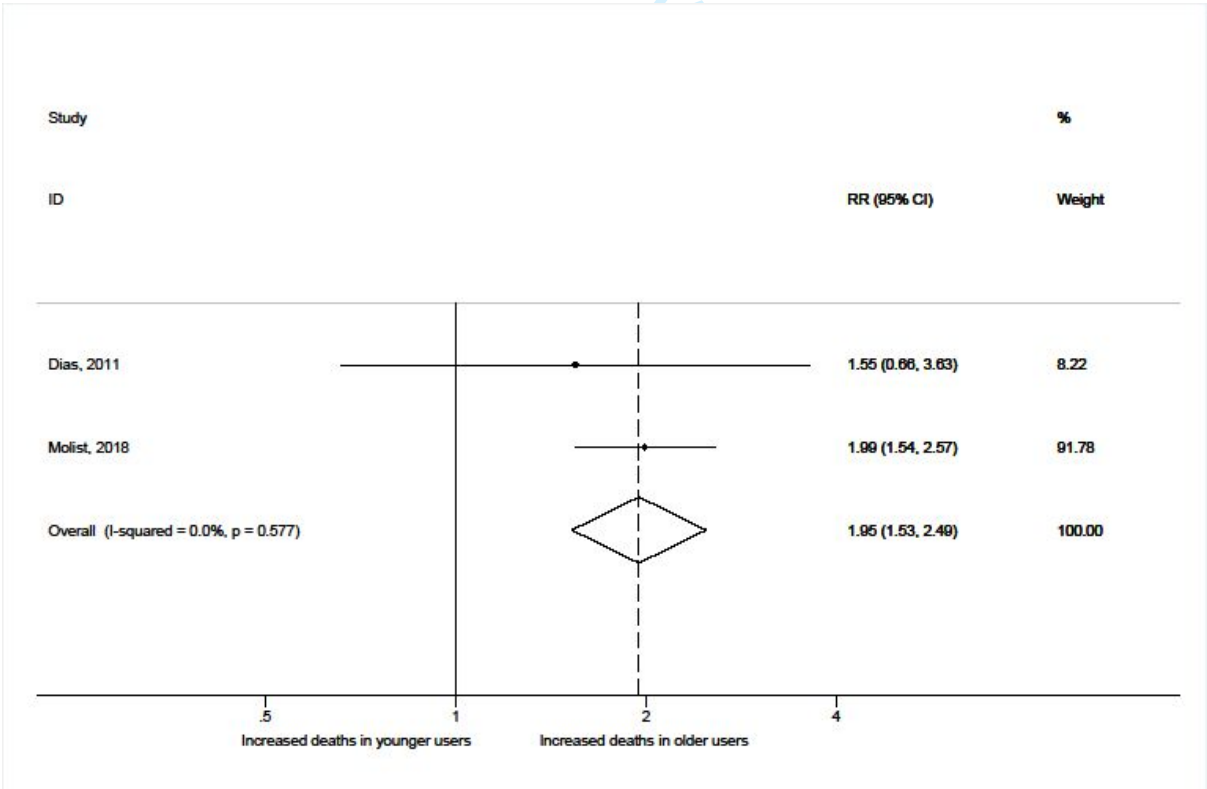
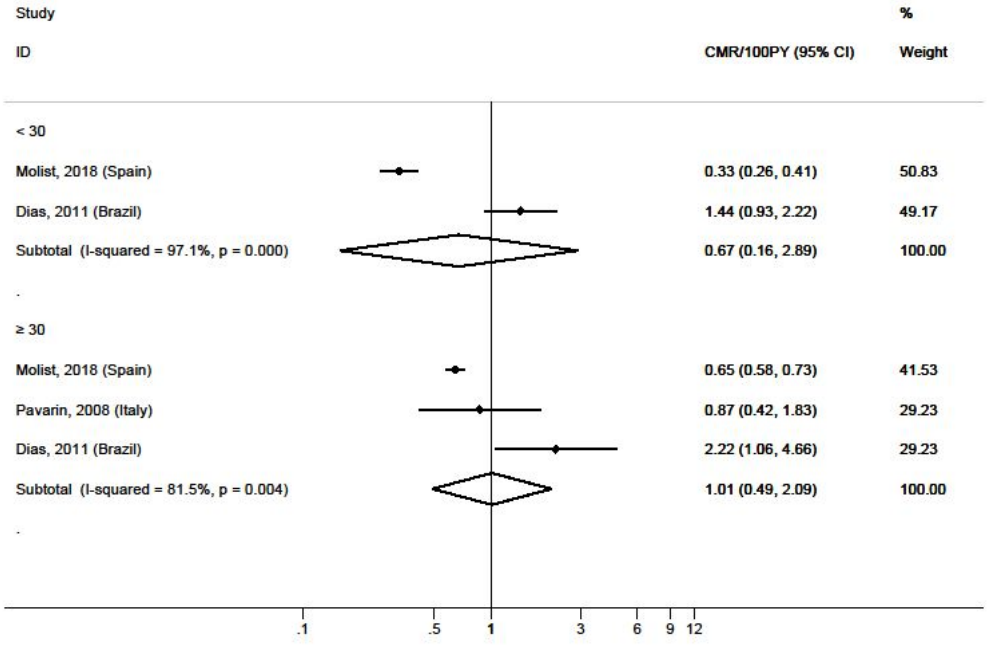


Figure L4. Forest plots derived from random effects meta-analysis for younger people (< 30) vs. older people (≥ 30) for all-cause CMR per 100 person-years (left) and all-cause SMR (right).



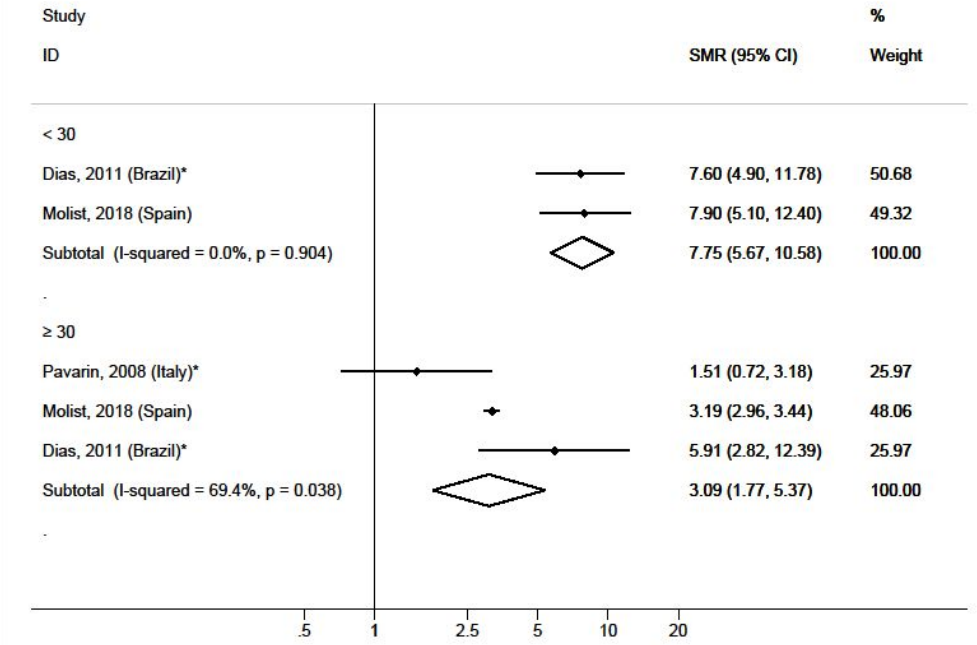
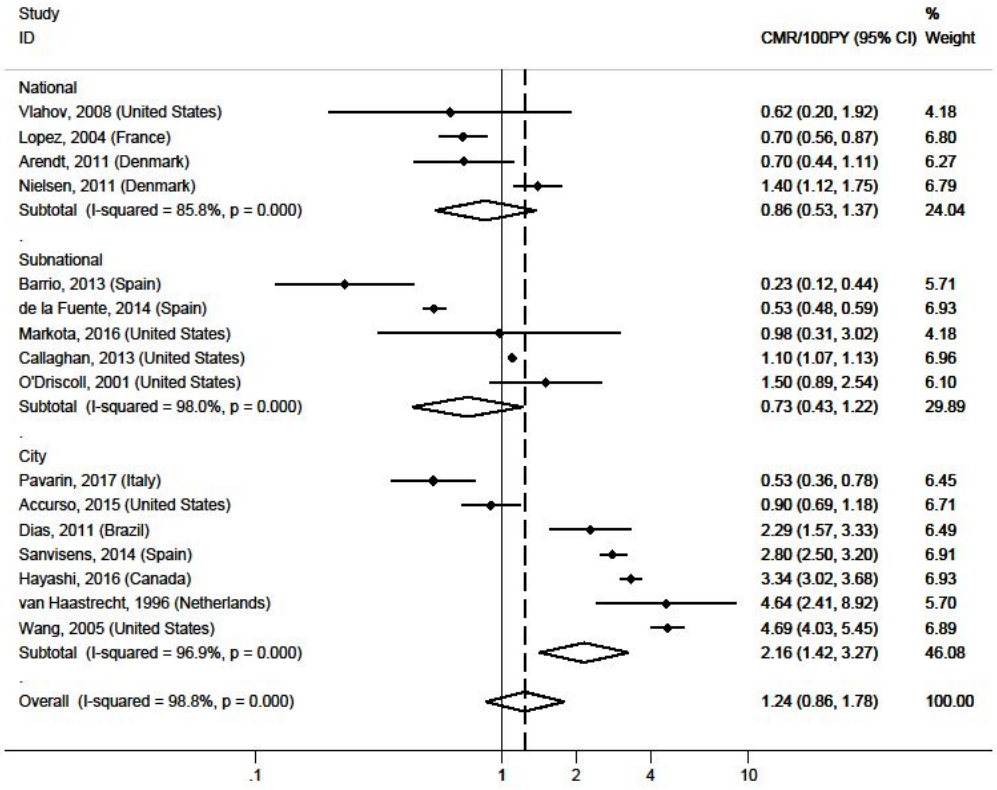


Figure L5. Forest plots derived from random effects meta-analysis by sampling frame: national vs. subnational (including states/provinces) vs. city for all-cause CMR per 100 person-years (left) and all-cause SMR (right).



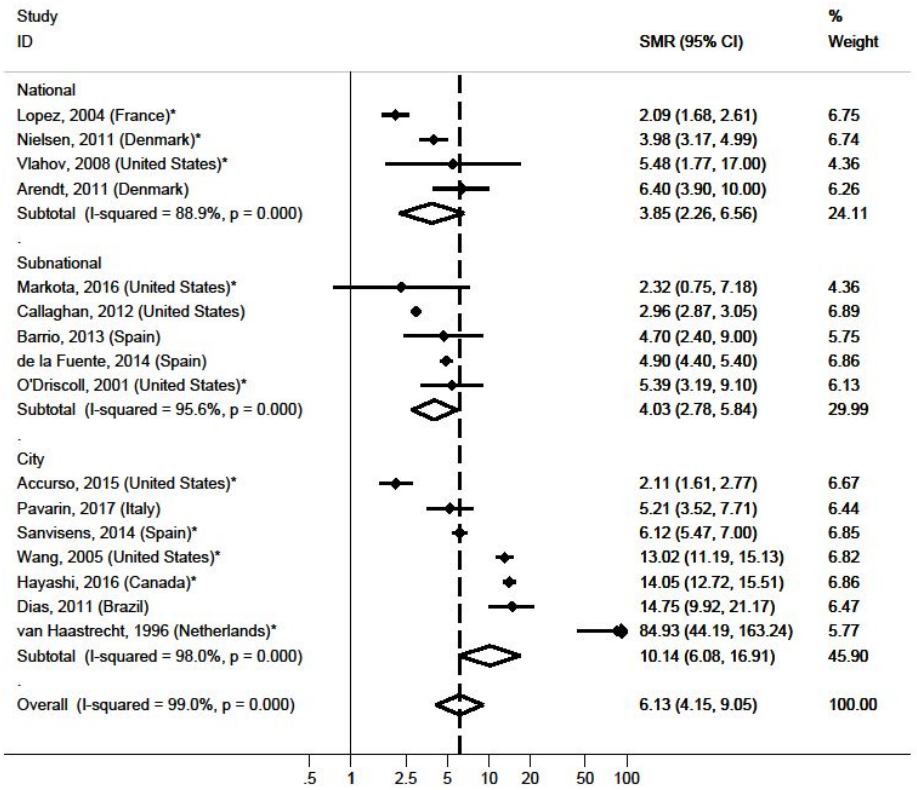
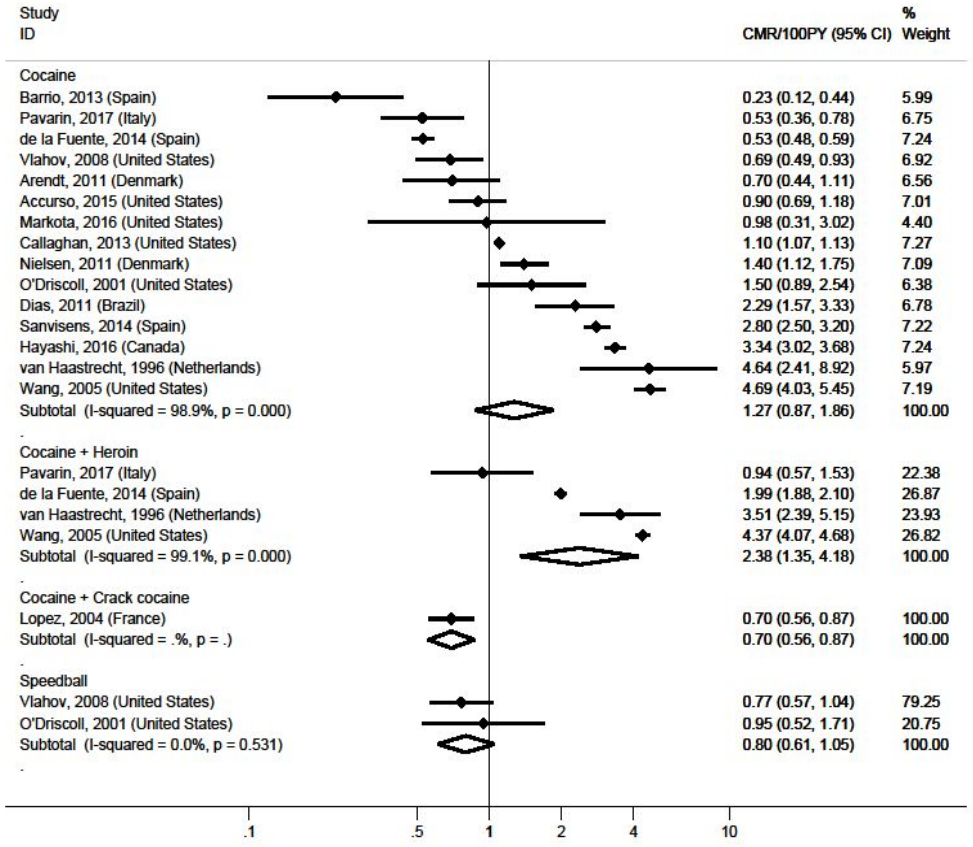


Figure L6. Forest plots derived from random effects meta-analysis by cocaine form used: cocaine vs. cocaine and crack cocaine vs. speedball vs. cocaine and heroin for all-cause CMR per 100 person-years (left) and all-cause SMR (right).



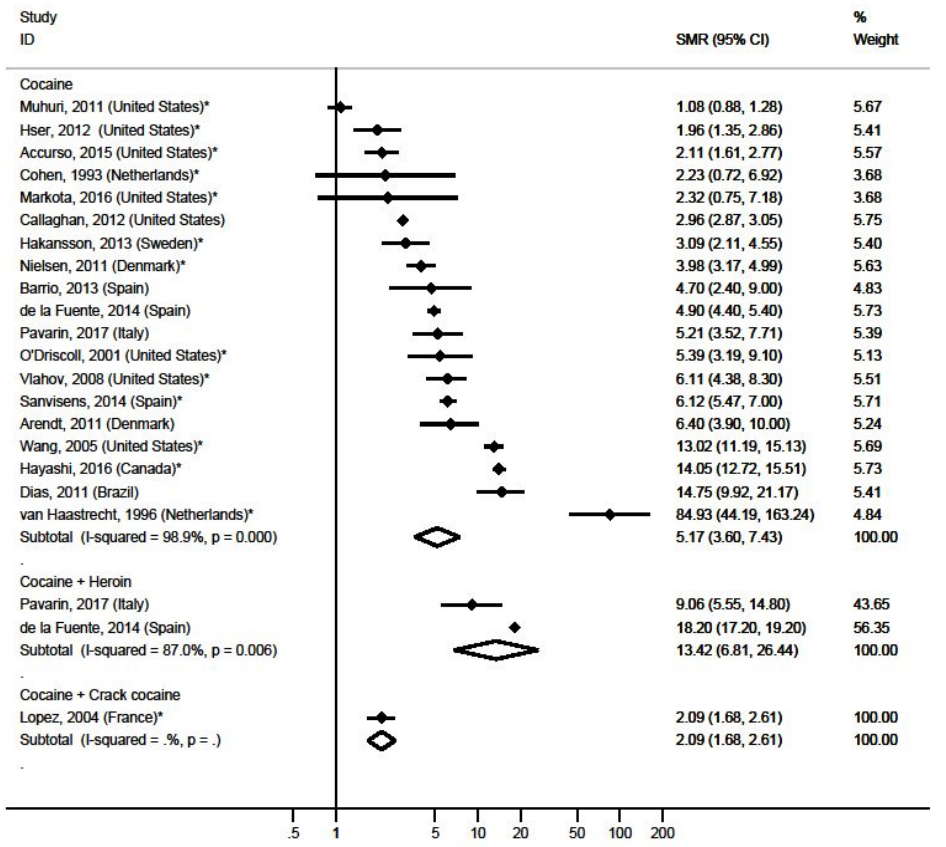


Figure L7. Bubble plot displaying results of meta-regression analysis examining the impact of proportion of women within cohort on CMR per 100PY.

```
Meta-regression                                 Number of obs  =       9
REML estimate of between-study variance         tau2           =   .9327
% residual variation due to heterogeneity       I-squared_res  =  99.11%
Proportion of between-study variance explained  Adj R-squared  =  -9.76%
With Knapp-Hartung modification
```

ln_cmr	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
prop_women	.1940122	.5429045	-0.59	0.576	.0002595	145.0524
_cons	1.717208	1.303015	0.71	0.499	.2854824	10.32919

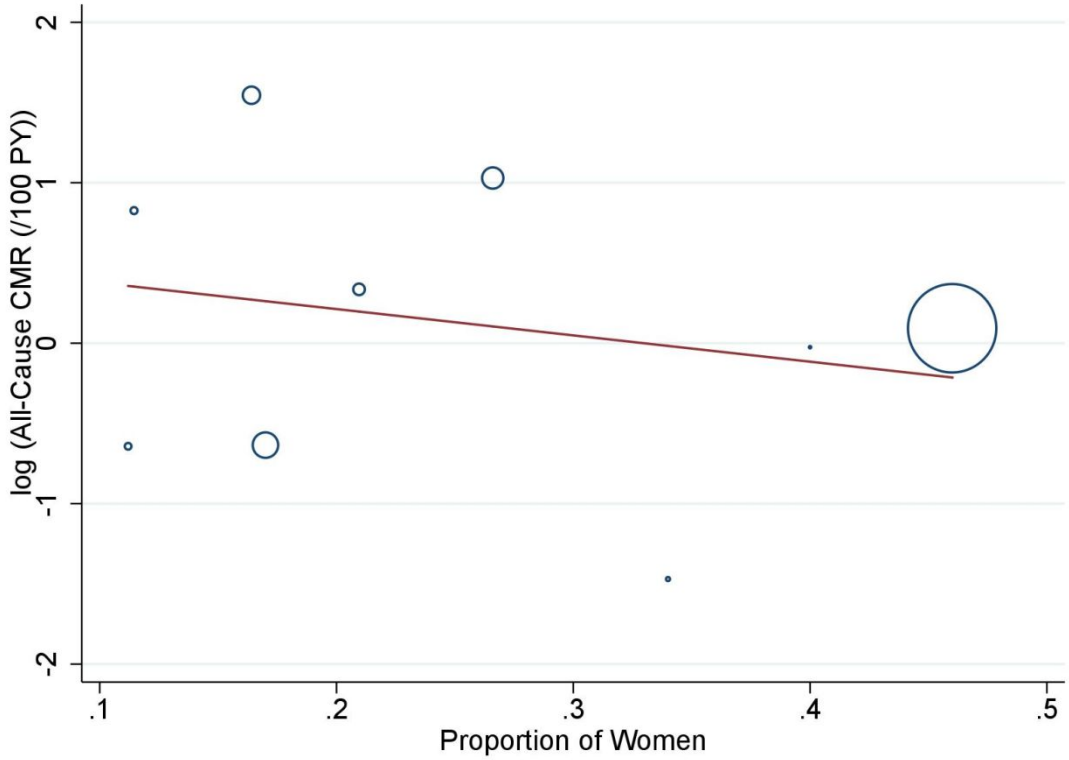


Figure L8. Bubble plot displaying results of meta-regression analysis examining the impact of proportion of people who inject drugs within cohort on CMR per 100PY.

```
Meta-regression                                 Number of obs  =       8
REML estimate of between-study variance         tau2           =   .2667
% residual variation due to heterogeneity       I-squared_res  =  92.04%
Proportion of between-study variance explained  Adj R-squared  =  68.62%
With Knapp-Hartung modification
```

ln_cmr	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
inject	5.870798	3.271986	3.18	0.019	1.501173	22.95955
_cons	.5090705	.2276331	-1.51	0.182	.1704495	1.520408

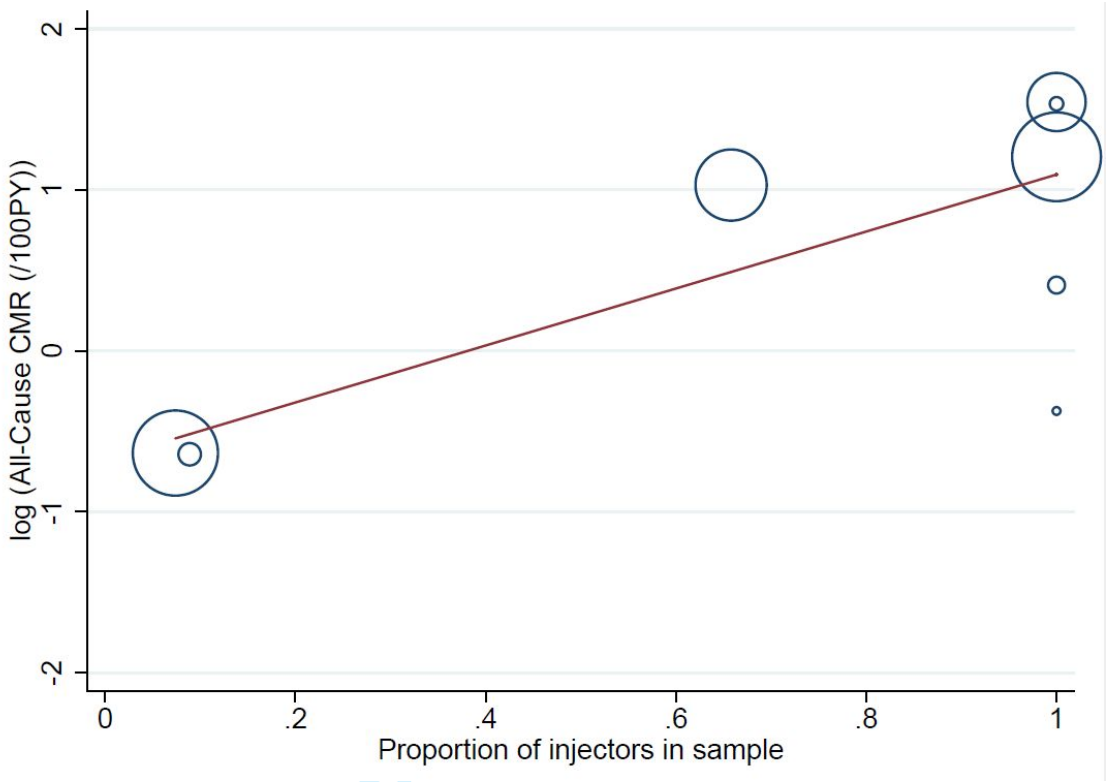


Figure L9. Meta-regression analysis examining the impact of cocaine form used (ref. Cocaine/Cocaine and Crack Cocaine; Cocaine 1 = Speedball/Cocaine and Heroin) on CMR per 100PY.

Meta-regression — Number of obs = 22
REML estimate of between-study variance — tau2 = .6419
% residual variation due to heterogeneity — I-squared_res = 98.82%
Proportion of between-study variance explained — Adj R-squared = -1.54%
With Knapp-Hartung modification

ln_cmrdrug	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
_In_cocaine_1	1.382652	.5461887	0.82	0.422	.6065223	3.151949
_cons	1.220997	.2533423	0.96	0.347	.7920386	1.882273

Figure L10. Meta-regression analysis output examining the impact of GBD region (ref. High-Income North America; GBD 1 = Western Europe, GBD 2 = Tropical Latin America) on CMR per 100PY.

Meta-regression — Number of obs = 16
REML estimate of between-study variance — tau2 = .6754
% residual variation due to heterogeneity — I-squared_res = 98.95%
Proportion of between-study variance explained — Adj R-squared = 1.20%
Joint test for all covariates — Model F(2,13) = 0.97
With Knapp-Hartung modification — Prob > F = 0.4048

ln_cmr	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
_In_GBD_1	1.689008	.7549208	1.17	0.262	.6430974	4.435951
_In_GBD_2	2.447457	2.199044	1.00	0.337	.3513243	17.0499
_cons	.9336222	.2803564	-0.23	0.823	.4880106	1.78613

Figure L11. Bubble plot displaying results of meta-regression analysis examining the impact of final year of study follow-up on CMR per 100PY.

Meta-regression — Number of obs = 16
REML estimate of between-study variance — tau2 = .5979
% residual variation due to heterogeneity — I-squared_res = 98.90%
Proportion of between-study variance explained — Adj R-squared = 12.54%
With Knapp-Hartung modification

ln_cmr	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
finalyear	.9385493	.0341406	-1.74	0.103	.8681087	1.014706
_cons	2.18e+55	1.59e+57	1.75	0.103	2.37e-13	2.0e+123

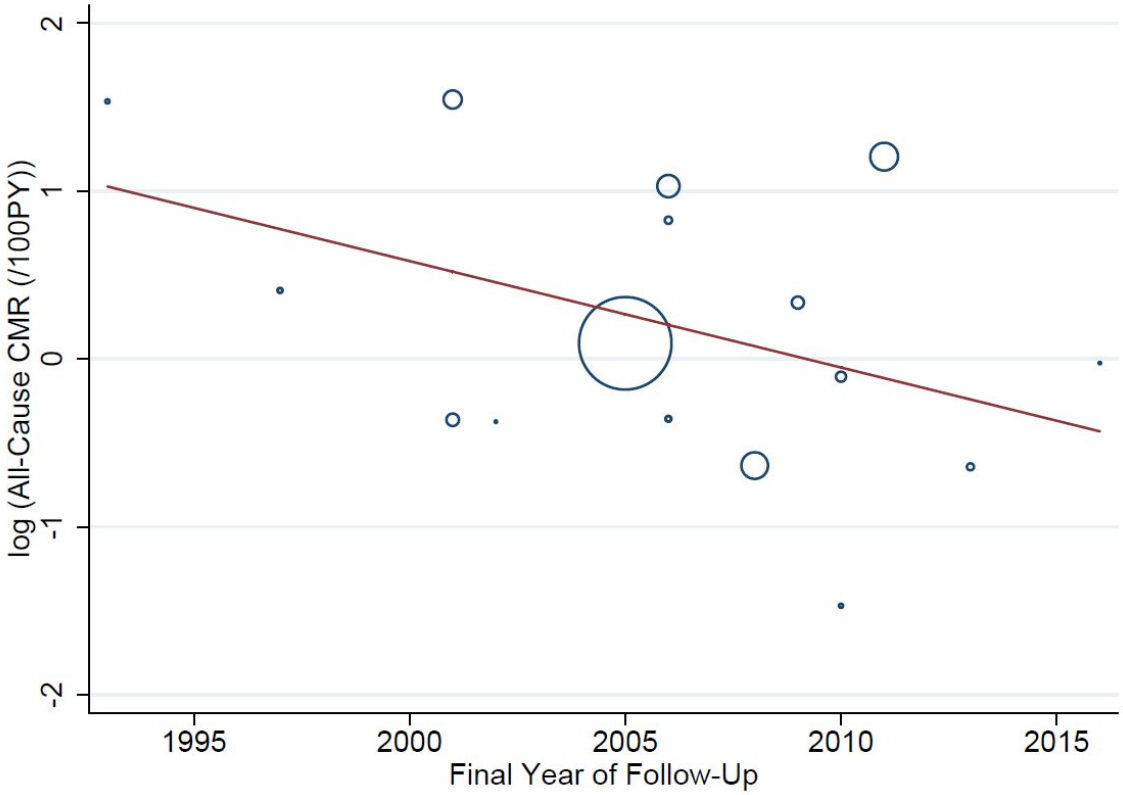


Figure L12. Bubble plot displaying results of meta-regression analysis examining the impact of cohort size on CMR per 100PY.

Meta-regression — Number of obs = 15
REML estimate of between-study variance — tau2 = .6731
% residual variation due to heterogeneity — I-squared_res = 98.70%
Proportion of between-study variance explained — Adj R-squared = -7.82%
With Knapp-Hartung modification

ln_cmr	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
sample	.9999954	.0000175	-0.26	0.797	.9999576	1.000033
_cons	1.163427	.2763392	0.64	0.535	.6964463	1.943527

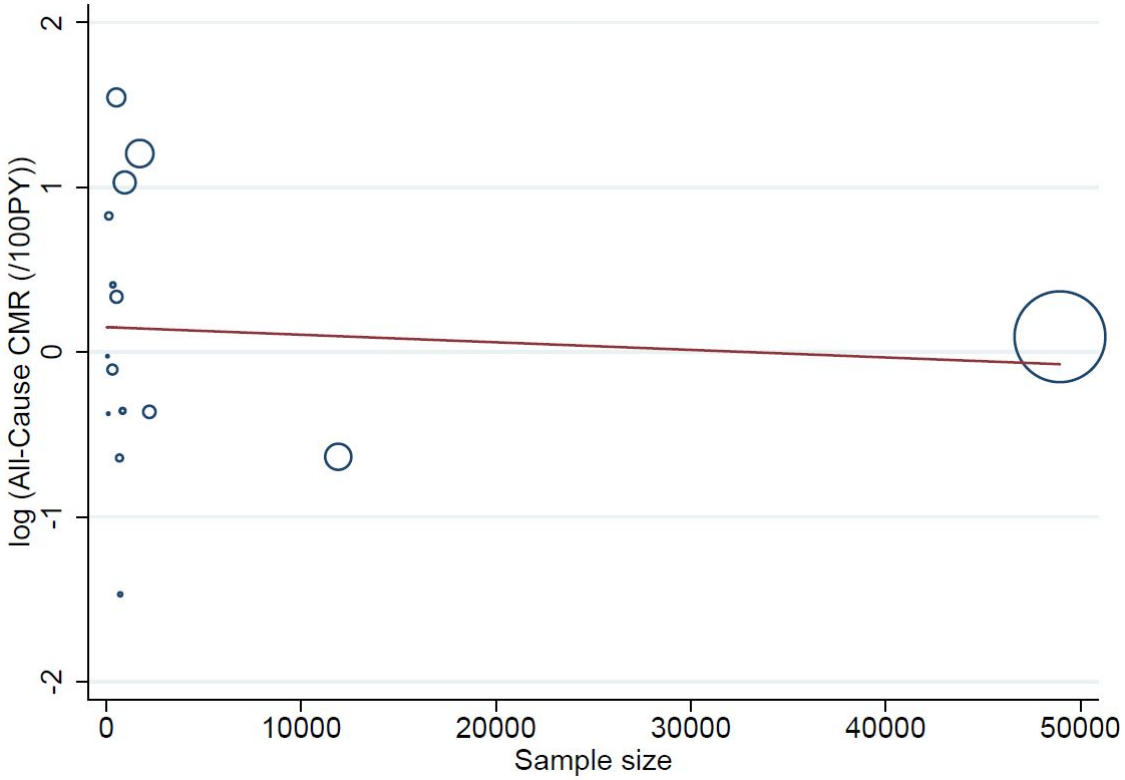


Figure L13. Bubble plot displaying results of meta-regression analysis examining the impact of person-years of follow-up on CMR per 100PY.

Meta-regression — Number of obs = 16
REML estimate of between-study variance — tau2 = .7278
% residual variation due to heterogeneity — I-squared_res = 98.79%
Proportion of between-study variance explained — Adj R-squared = -6.45%
With Knapp-Hartung modification

ln_cmr	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
lengthFU	1.014049	.0376479	0.38	0.713	.9364332	1.098097
_cons	1.023937	.5541067	0.04	0.966	.3207789	3.268441

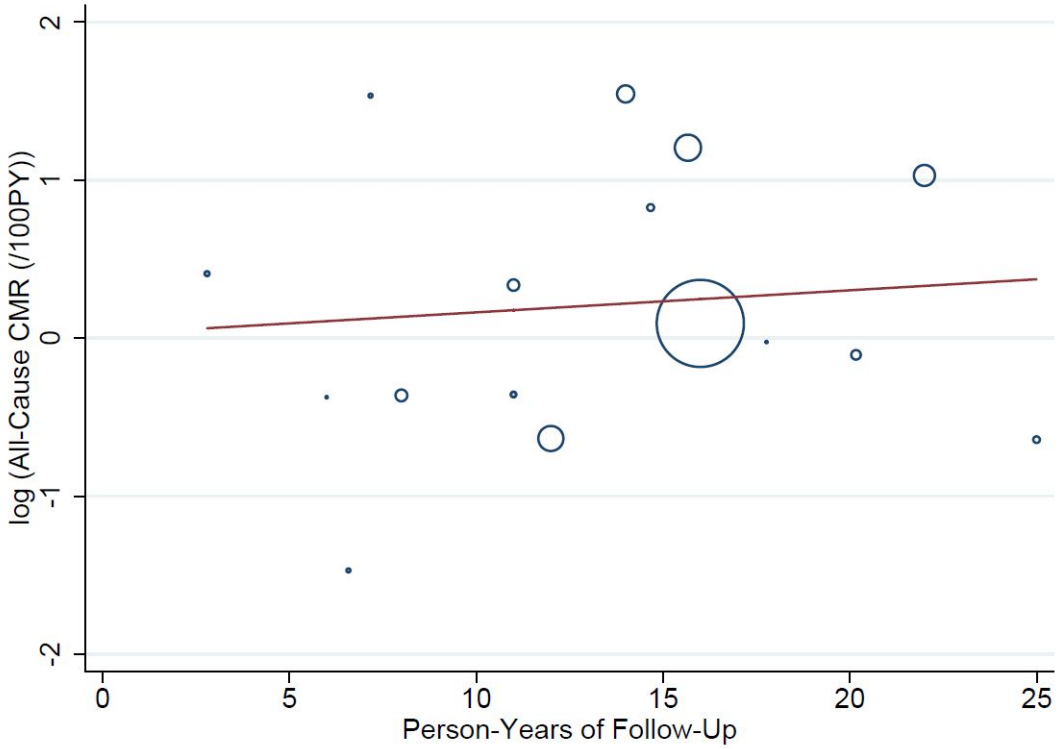


Figure L14. Meta-regression analysis examining the impact of recruitment setting (ref. Treatment clinics and other health services; Setting 1 = Hospital; Setting 2 = Convenience sampling) on CMR per 100PY.

```
Meta-regression                                 Number of obs  =      16
REML estimate of between-study variance         tau2           =   .7836
% residual variation due to heterogeneity       I-squared_res  =  98.33%
Proportion of between-study variance explained  Adj R-squared  = -14.62%
Joint test for all covariates                   Model F(2,13)  =    0.10
With Knapp-Hartung modification                 Prob > F       =  0.9036
```

ln_cmr	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
_In_setting_1	.7503937	.4920517	-0.44	0.669	.1819971	3.093954
_In_setting_2	.9611738	.4889236	-0.08	0.939	.320292	2.884415
_cons	1.319066	.4887616	0.75	0.468	.5924015	2.937088

Figure L15. Meta-regression analysis output examining the impact of study sampling frame (ref. National/Subnational, Area 2 = City) on CMR per 100PY.

```
Meta-regression                                 Number of obs  =      16
REML estimate of between-study variance         tau2           =   .4449
% residual variation due to heterogeneity       I-squared_res  =  96.64%
Proportion of between-study variance explained  Adj R-squared  =  34.92%
With Knapp-Hartung modification
```

ln_cmr	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
_In_area_2	2.776357	.9854761	2.88	0.012	1.296724	5.944331
_cons	.7759408	.1873406	-1.05	0.311	.4623147	1.302325

Figure L16. Bubble plot displaying results of meta-regression analysis examining the impact of proportion of women within cohort on SMR.

Meta-regression — Number of obs = 9
REML estimate of between-study variance — tau2 = .1861
% residual variation due to heterogeneity — I-squared_res = 95.11%
Proportion of between-study variance explained — Adj R-squared = 39.96%
With Knapp-Hartung modification

ln_smr	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
prop_women	.0375019	.0505811	-2.43	0.045	.0015451	.9102363
_cons	12.45751	4.452131	7.06	0.000	5.350775	29.00318

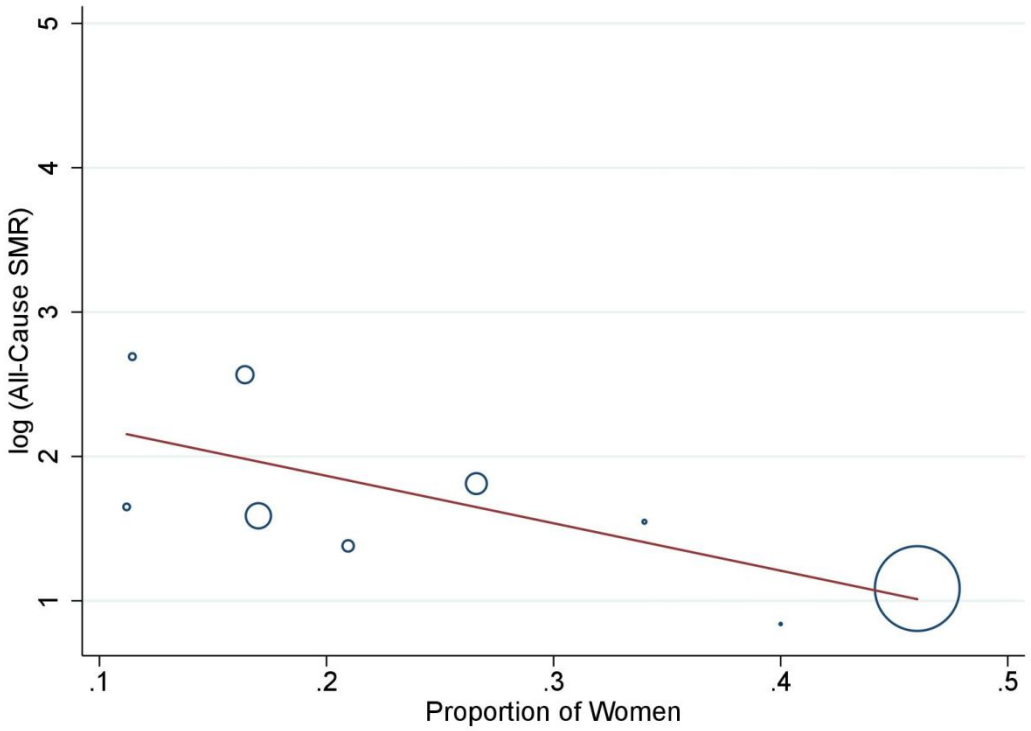


Figure L17. Bubble plot displaying results of meta-regression analysis examining the impact of proportion of people who inject drugs within cohort on SMR.

Meta-regression — Number of obs = 8
REML estimate of between-study variance — tau2 = .68
% residual variation due to heterogeneity — I-squared_res = 92.70%
Proportion of between-study variance explained — Adj R-squared = 17.35%
With Knapp-Hartung modification

ln_smr	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
inject	3.090519	2.472367	1.41	0.208	.4364191	21.88563
_cons	4.279761	2.78444	2.23	0.067	.8710296	21.02839

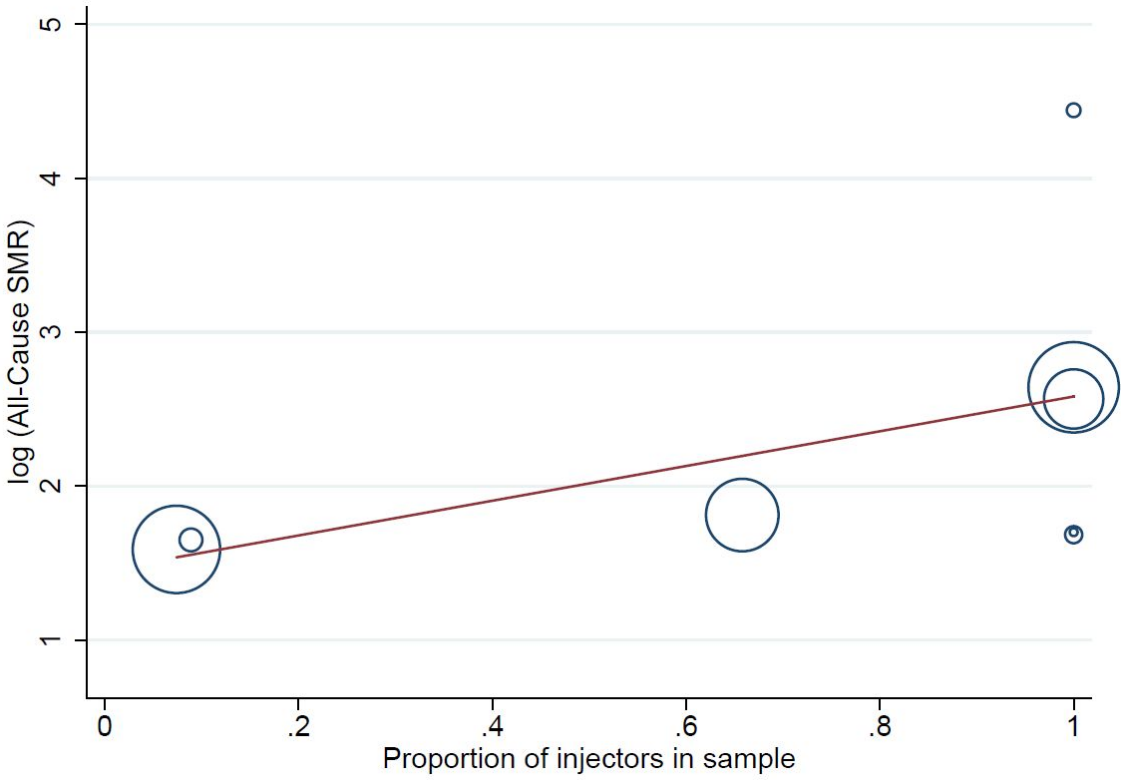


Figure L18. Meta-regression analysis examining the impact of cocaine form used (ref. Cocaine/Cocaine and Crack Cocaine; Cocaine 1 = Cocaine and Heroin) on SMR.

Meta-regression — Number of obs = 18
REML estimate of between-study variance — tau2 = .7204
% residual variation due to heterogeneity — I-squared_res = 98.91%
Proportion of between-study variance explained — Adj R-squared = 2.50%
With Knapp-Hartung modification

ln_smrdrug	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
_In_cocaine_1	2.113077	1.400303	1.13	0.276	.5185684	8.610423
_cons	6.164663	1.374622	8.16	0.000	3.842519	9.890144

Figure L19. Meta-regression analysis output examining the impact of GBD region (ref. High-Income North America; GBD 1 = Western Europe, GBD 2 = Tropical Latin America) on CMR per 100PY.

Meta-regression — Number of obs = 16
REML estimate of between-study variance — tau2 = .8346
% residual variation due to heterogeneity — I-squared_res = 99.02%
Proportion of between-study variance explained — Adj R-squared = -7.77%
Joint test for all covariates — Model F(2,13) = 0.56
With Knapp-Hartung modification — Prob > F = 0.5870

ln_smr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
_In_GBD_1	-.207001	.4939925	-0.42	0.682	-1.274207	.8602048
_In_GBD_2	.8438148	.9954567	0.85	0.412	-1.306739	2.994368
_cons	1.847706	.3326572	5.55	0.000	1.129044	2.566368

Figure L20. Bubble plot displaying results of a meta-regression analysis examining impact of final year of study follow-up on SMR.

Meta-regression — Number of obs = 16
REML estimate of between-study variance — tau2 = .6437
% residual variation due to heterogeneity — I-squared_res = 98.86%
Proportion of between-study variance explained — Adj R-squared = 16.88%
With Knapp-Hartung modification

ln_smr	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
finalyear	.9248289	.0347346	-2.08	0.056	.8532522	1.00241
_cons	7.30e+68	5.50e+70	2.10	0.054	.0490549	1.1e+139

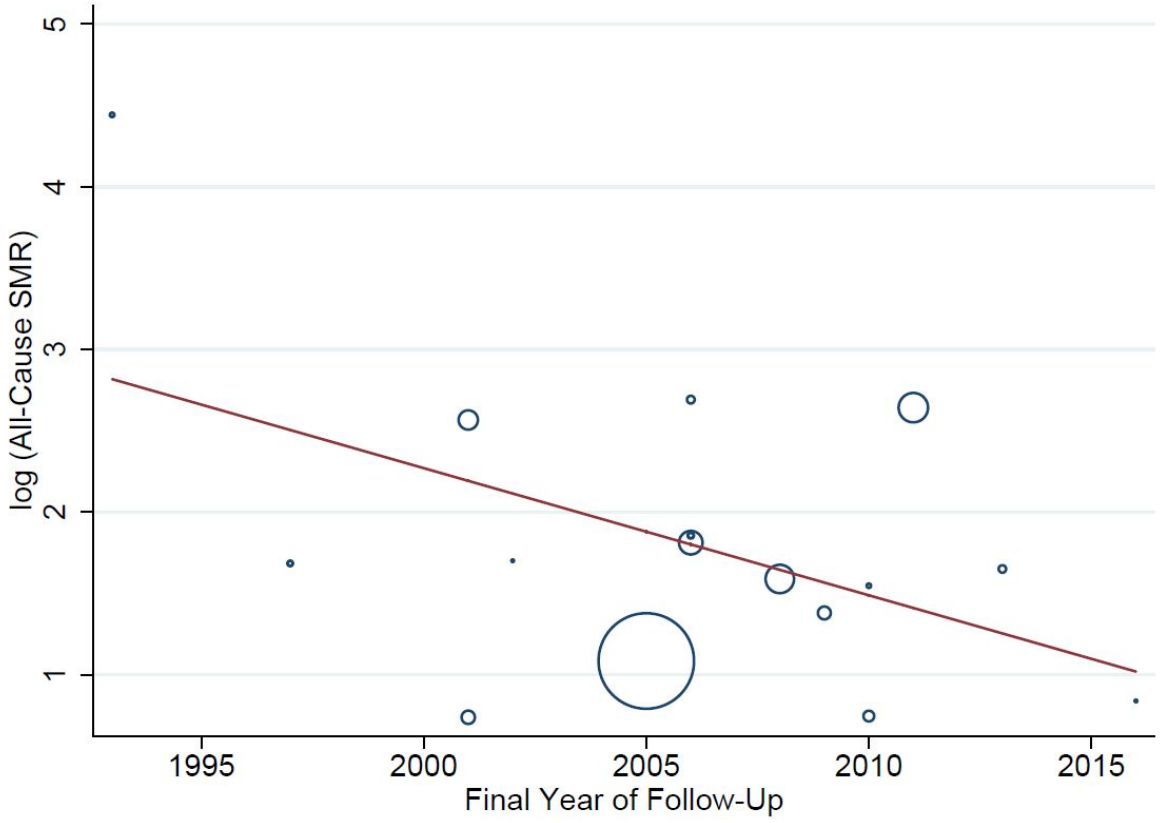


Figure L21. Bubble plot displaying results of a meta-regression analysis examining impact of cohort size of follow-up on SMR.

Meta-regression — Number of obs = 15
REML estimate of between-study variance — tau2 = .3926
% residual variation due to heterogeneity — I-squared_res = 97.42%
Proportion of between-study variance explained — Adj R-squared = 0.29%
With Knapp-Hartung modification

ln_smr	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
sample	.9999869	.0000134	-0.98	0.345	.9999579	1.000016
_cons	5.615114	1.04373	9.28	0.000	3.758032	8.389898

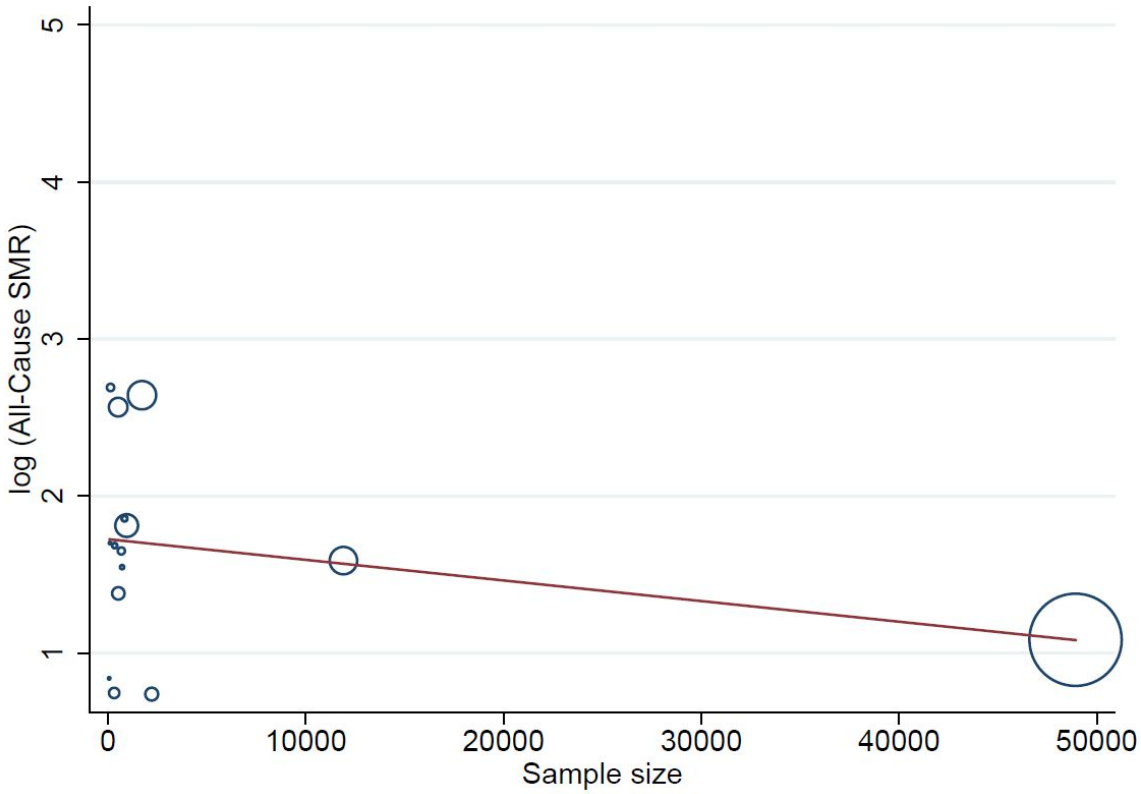


Figure L22. Bubble plot displaying results of a meta-regression analysis examining impact of person-years of follow-up on SMR.

Meta-regression — Number of obs = 16
REML estimate of between-study variance — tau2 = .8104
% residual variation due to heterogeneity — I-squared_res = 99.04%
Proportion of between-study variance explained — Adj R-squared = -4.64%
With Knapp-Hartung modification

ln_smr	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
lengthFU	.9733267	.0381837	-0.69	0.502	.8947816	1.058767
_cons	8.785405	5.019797	3.80	0.002	2.579526	29.92152

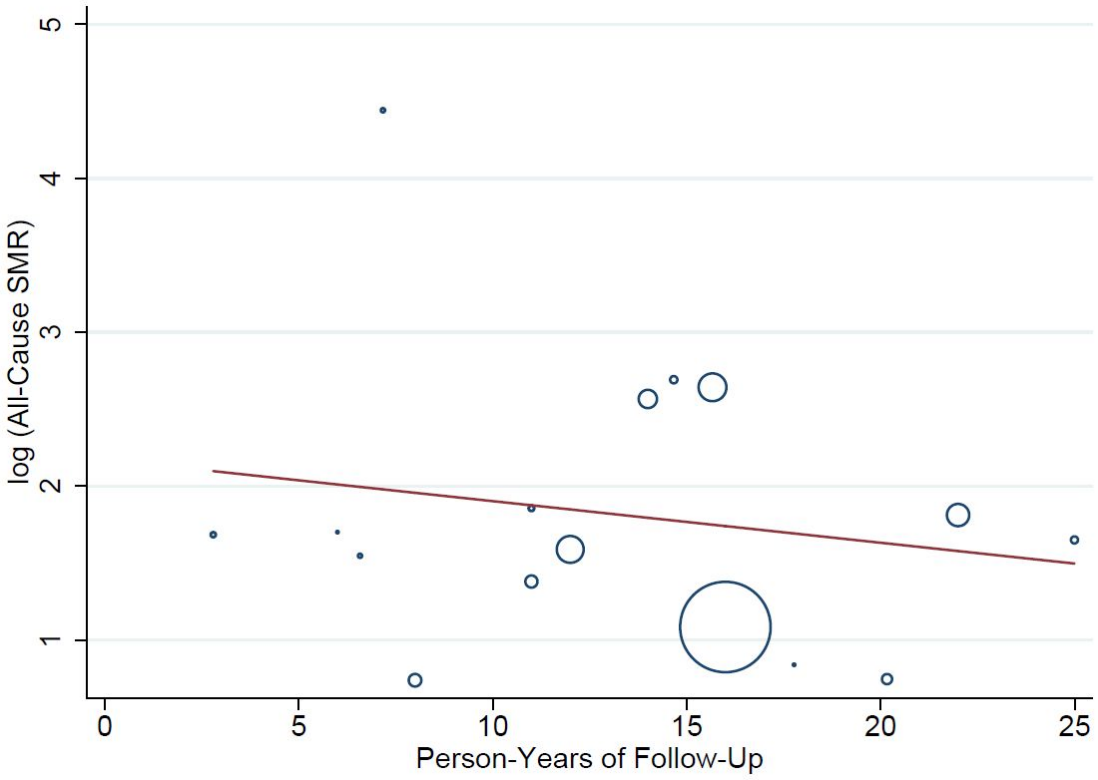


Figure L23. Meta-regression analysis examining the impact of recruitment setting (ref. Treatment clinics and other health services; Setting 1 = Hospital; Setting 2 = Convenience sampling) on SMR.

```
Meta-regression                                 Number of obs   =        16
REML estimate of between-study variance         tau2            =     .6217
% residual variation due to heterogeneity       I-squared_res   =    96.99%
Proportion of between-study variance explained  Adj R-squared   =    19.73%
Joint test for all covariates                   Model F(2,13)   =     2.83
With Knapp-Hartung modification                 Prob > F        =   0.0953
```

ln_smr	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
_In_setting_1	.2472893	.1457852	-2.37	0.034	.0691965	.8837443
_In_setting_2	.5868937	.2679143	-1.17	0.264	.2189067	1.573475
_cons	9.93503	3.299796	6.91	0.000	4.847812	20.3607

Figure L24. Meta-regression analysis output examining the impact of study sampling frame (ref. National/Subnational, Area 2 = City) on SMR.

```
Meta-regression                                 Number of obs   =        16
REML estimate of between-study variance         tau2            =     .5835
% residual variation due to heterogeneity       I-squared_res   =    96.65%
Proportion of between-study variance explained  Adj R-squared   =    24.65%
With Knapp-Hartung modification
```

ln_smr	exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
_In_area_2	2.578813	1.042046	2.34	0.034	1.084008	6.1349
_cons	3.971081	1.086776	5.04	0.000	2.20796	7.142107

References:

1. Cunningham R, Walton MA, Weber JE, et al. One-Year Medical Outcomes and Emergency Department Recidivism After Emergency Department Observation for Cocaine-Associated Chest Pain. *Annals of Emergency Medicine* 2009; **53**(3): 310-20.
2. Egbuche O, Ekechukwu I, Maduabum N, Obinwa U, Ukpaka K, Onwuanyi A. Effect of beta-blocker therapy on readmissions and mortality in heart failure patients with ongoing cocaine use. *Journal of Invasive Cardiology* 2017; **29** (10): E111.
3. Nguyen P, Kamran H, Nasir S, et al. Comparison of Frequency of Cardiovascular Events and Mortality in Patients With Heart Failure Using Versus Not Using Cocaine. *Am J Cardiol* 2017; **119**(12): 2030-4.
4. Peralta R, Yoon A, Atoui M, et al. Efficacy of cardiac computerized tomographic angiography in the evaluation of patients with cocaine-induced chest pain: A pilot randomized trial. *Circulation Conference: American Heart Association's* 2014; **130**(Supplement 2): A18655.
5. Campa A, Martinez SS, Sherman KE, et al. Cocaine use and liver disease are associated with all-cause mortality in the Miami adult studies in HIV (MASH) cohort *Journal of Drug Abuse* 2016; **2**(4).
6. Nacher M, Adenis A, Hanf M, et al. Crack cocaine use increases the incidence of AIDS-defining events in French Guiana. *AIDS* 2009; **23**(16): 2223-6.
7. Weber E, Huber M, Battegay M, et al. Influence of noninjecting and injecting drug use on mortality, retention in the cohort, and antiretroviral therapy, in participants in the Swiss HIV Cohort Study *HIV Medicine* 2015; **16**(3): 137-51.
8. Jones ME, Swerdlow AJ. Bias in the standardized mortality ratio when using general population rates to estimate expected number of deaths. *Am J Epidemiol* 1998; **148**(10): 1012-7.
9. Barrio G, Molist G, de la Fuente L, et al. Mortality in a cohort of young primary cocaine users: Controlling the effect of the riskiest drug-use behaviors. *Addictive Behaviors* 2013; **38**(3): 1601-4.
10. Callaghan RC, Gatley JM, Veldhuizen S, Lev-Ran S, Mann R, Asbridge M. Alcohol- or drug-use disorders and motor vehicle accident mortality: a retrospective cohort study. *Accident; analysis and prevention* 2013; **53**: 149-55.
11. Hayashi K, Dong H, Marshall BD, et al. Sex-Based Differences in Rates, Causes, and Predictors of Death Among Injection Drug Users in Vancouver, Canada. *American Journal of Epidemiology* 2016; **183**(6): 544-52.
12. Lopez D, Martineau H, Palle C. Mortality of individuals arrested for heroin, cocaine or crack use, 2004.
13. Sanvisens A, Vallecillo G, Bolao F, et al. Temporal trends in the survival of drug and alcohol abusers according to the primary drug of admission to treatment in Spain. *Drug and Alcohol Dependence* 2014; **136**(1): 115-20.
14. Accurso AJ, Rastegar DA, Ghazarian SR, Fingerhood MI. Impact of hepatitis C status on 20-year mortality of patients with substance use disorders. *Addiction science & clinical practice* 2015; **10**(20): 1-8.
15. Arendt M, Munk-Jorgensen P, Sher L, Jensen SOW. Mortality among individuals with cannabis, cocaine, amphetamine, MDMA, and opioid use disorders: A nationwide follow-up study of Danish substance users in treatment. *Drug and Alcohol Dependence* 2011; **114**(2-3): 134-9.
16. Bohnert KM, Ilgen MA, Louzon S, McCarthy JF, Katz IR. Substance use disorders and the risk of suicide mortality among men and women in the US Veterans Health Administration. *Addiction* 2017; **112**(7): 1193-201.
17. Callaghan RC, Cunningham JK, Verdichevski M, Sykes J, Jaffer SR, Kish SJ. All-cause mortality among individuals with disorders related to the use of methamphetamine: A comparative cohort study. *Drug and Alcohol Dependence* 2012; **125**(3): 290-4.
18. de la Fuente L, Molist G, Espelt A, et al. Mortality risk factors and excess mortality in a cohort of cocaine users admitted to drug treatment in Spain. *Journal of Substance Abuse Treatment* 2014; **46**(2): 219-26.

19. Brugal M, Molist G, Sarasa-Renedo A, et al. Assessing gender disparities in excess mortality of heroin or cocaine users compared to the general population. *International Journal of Drug Policy* 2016; **38**: 36-42.
20. Molist G, Brugal MT, Barrio G, et al. Effect of ageing and time since first heroin and cocaine use on mortality from external and natural causes in a Spanish cohort of drug users. *International Journal of Drug Policy* 2018; **53**: 8-16.
21. Colell E, Domingo-Salvany A, Espelt A, Pares-Badell O, Brugal MT. Differences in mortality in a cohort of cocaine use disorder patients with concurrent alcohol or opiates disorder. *Addiction* 2018; **113**(6): 1045-55.
22. Dias AC, Araujo MR, Dunn J, Sesso RC, de Castro V, Laranjeira R. Mortality rate among crack/cocaine-dependent patients: A 12-year prospective cohort study conducted in Brazil. *Journal of Substance Abuse Treatment* 2011; **41**(3): 273-8.
23. Gossop M, Stewart D, Treacy S, Marsden J. A prospective study of mortality among drug misusers during a 4-year period after seeking treatment. *Addiction* 2002; **97**(1): 39-47.
24. Tyndall MW, Craib KJP, Currie S, Li K, O'Shaughnessy MV, Schechter MT. Impact of HIV infection of mortality in a cohort of injection drug users. *Journal of Acquired Immune Deficiency Syndrome* 2001; **28**(4): 351-7.
25. Hser YI, Kagihara J, Huang D, Evans E, Messina N. Mortality among substance-using mothers in California: a 10-year prospective study. *Addiction* 2012; **107**(1): 215-22.
26. Markota M, Croarkin PE, Bobo WV. Increased 5-year all-cause mortality in youth with positive urine cocaine drug screens. *Journal of the American Academy of Child and Adolescent Psychiatry* 2016; **55 (10 Supplement 1)**: S148.
27. Martell BA, Orson FM, Poling J, et al. Cocaine vaccine for the treatment of cocaine dependence in methadone-maintained patients: A randomized, double-blind, placebo-controlled efficacy trial. *Archives of General Psychiatry* 2009; **66**(10): 1116-23.
28. Nielsen SF, Hjorthoj CR, Erlangsen A, Nordentoft M. Psychiatric disorders and mortality among people in homeless shelters in Denmark: A nationwide register-based cohort study. *The Lancet* 2011; **377**(9784): 2205-14.
29. O'Driscoll PT, McGough J, Hagan H, Thiede H, Critchlow C, Alexander ER. Predictors of accidental fatal drug overdose among a cohort of injection drug users. *American Journal of Public Health* 2001; **91**(6): 984-7.
30. Pavarin RM, Fioritti A. Mortality Trends among Cocaine Users Treated between 1989 and 2013 in Northern Italy: Results of a Longitudinal Study. *Journal of Psychoactive Drugs* 2017; **50**(1): 72-80.
31. Pavarin RM. Cocaine consumption and death risk: A follow-up study on 347 cocaine addicts in the metropolitan area of Bologna. *Annali-Istituto Superiore di Sanita* 2008; **44**(1): 91-8.
32. Pavarin RM. Mortality risk for cocaine abusers in relation to heroin use: A follow-up study. *Substance Use & Misuse* 2013; **48**(9): 702-10.
33. Ryb GE, Cooper CC, Dischinger PC, Kufera JA, Auman KM, Soderstrom CA. Suicides, homicides, and unintentional injury deaths after trauma center discharge: Cocaine use as a risk factor. *Journal of Trauma - Injury, Infection and Critical Care* 2009; **67**(3): 490-6.
34. van Haastrecht HJA, van Ameijden EJC, van den Hoek JAR, Mientjes GHC, Bax JS, Coutinho RA. Predictors of mortality in the Amsterdam cohort of human immunodeficiency virus (HIV)-positive and HIV-negative drug users. *American Journal of Epidemiology* 1996; **143**(4): 380-91.
35. Vlahov D, Wang C, Ompad D, et al. Mortality risk among recent-onset injection drug users in five U.S. cities. *Subst Use Misuse* 2008; **43**(3-4): 413-28.
36. Wang C, Vlahov D, Galai N, et al. The effect of HIV infection on overdose mortality. *AIDS* 2005; **19**(9): 935-42.
37. Jones AA, Vila-Rodriguez F, Leonova O, et al. Mortality from treatable illnesses in marginally housed adults: A prospective cohort study. *BMJ Open* 2015; **5 (8) (no pagination)**(e008876): e008876.